2,4-DINITROTOLUENE

CAS No: 121-14-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	182.14
Boiling point	300°C
Melting point	71°C
Vapor pressure	0.00014 mm Hg @ 25°C
Air concentration conversion	1 ppm = 7.4 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 8.9 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 3.1 E-1 $(mg/kg\text{-}day)^{-1}$
[calculated from a potency factor derived by US EPA (1987) and adopted by CDHS (see Final Statement of Reasons)]

III. CARCINOGENIC EFFECTS

Human Studies

No data are available addressing the carcinogenicity of 2,4-dinitrotoluene (2,4-DNT) in humans.

Animal Studies

Lee *et al.* (1978) exposed male and female CD rats to practical grade 2,4-DNT in feed at concentrations of 0, 15, 100, and 700 ppm for 720 days. Animals were sacrificed at 750 days. Decreased weight gain and lifespan were observed among animals in the highest treatment group. Noncancer toxic effects observed included toxic anemia and aspermatogenesis. Tumors observed included fibromas of the connective tissue of male rats and fibroadenoma of the mammary gland of female rats. The incidence data for liver and mammary tumors in female rats are presented in Table 1. Significantly increased incidence was found in the highest dose group for liver tumors ($p = 4 \times 10^{-4}$; Fisher's exact test), mammary gland tumors ($p = 1.75 \times 10^{-4}$), and combined mammary gland and liver tumors ($p = 7 \times 10^{-5}$). Mammary tumor incidence among male rats was 1/37, 0/37, 0/29, and 17/23 in the 0, 15, 100, and 700 ppm 2,4-DNT dose groups, respectively. Only the highest dose group showed significantly increased tumor incidence ($p = 4 \times 10^{-9}$).

Table 1. Incidence of liver and mammary gland tumors among female CD rats exposed to practical grade 2,4-dinitrotoluene (2,4-DNT) in feed for 24 months (Lee *et al.*, 1978).

treatment level (ppm)	tumor incidence		
	liver[1]	mammary gland[2]	combined
0	0/31	11/31	11/31
15	3/43	12/43	13/43
100	3/35	18/35	18/35
700	30/42	34/43	35/43

[1] Tumor incidence includes neoplastic nodules and hepatocellular carcinoma of the liver.
[2] Tumor incidence includes adenoma, fibroadenoma, fibroma, or adenocarcinoma of the mammary gland.

The National Cancer Institute (NCI, 1978) conducted a study exposing Fischer rats and $B6C3F_1$ mice to practical-grade 2,4-DNT (>95% pure). Male and female Fischer rats (50/sex/group) were exposed to feed containing 0.02% or 0.008% 2,4-DNT (time-weighted concentrations). Control groups consisted of 25 rats/sex for the high-dose group and 50 rats/sex for the low-dose group. The treatment period was 78 weeks long and the observation period continued for 26 weeks. Among treated male rats in both high- and low-dose groups, the incidence of benign fibroma of the skin and subcutaneous tissue was increased over controls (high-dose: 13/49 treated vs. 0/25 control, $p = 0.003$; low-dose: 7/49 treated vs. 0/46 control, $p = 0.008$ by Fisher's exact test). Among treated female rats in the high-dose group, the incidence of fibroadenoma of the mammary gland was increased over control animals (23/50 treated vs. 4/23 control, $p = 0.016$).

In the same study (NCI, 1978), male and female $B6C3F_1$ mice (50/sex/group) were treated with diet containing 0.04% or 0.008% 2,4-DNT (time-weighted concentrations). Groups of 50 mice/sex served as controls for the high- and low-dose groups. The treatment period lasted 78 weeks and the animals were observed for an additional 13 weeks. No significant increase in tumor incidence was observed among treated animals.

Ellis *et al.* (1979) (also reported by Lee *et al.*,1985) exposed male and female CD (Sprague-Dawley) rats (38/sex/group) to 0, 15, 100, or 700 ppm 2,4-DNT in feed. At 12 months, 8 rats/group were sacrificed for necropsy; the remainder were sacrificed at 24 months. Cumulative deaths during the course of the study ranged from 55 to 100% in male rats and 60 to 97% in female rats, including control animals. Histopathological outcomes of animals that died during the course of the experiment (but after 52 weeks) were included in the final incidence data along with the incidence data among survivors. Tumors showing statistically significant increases ($p<0.05$ by Fisher's exact test) were hepatocellular carcinomas and mammary gland tumors among female rats in the highest dose group. Hepatocellular carcinomas were reported in 18/34 treated high-dose female rats vs. 0/23 control rats ($p = 4.3 \times 10^{-6}$). Mammary gland tumors, including both benign and malignant tumors of epithelial or mesenchymal origin, were reported in 33/35 treated high-dose female rats vs. 11/23 control rats ($p < 0.0001$).

Ellis *et al.*(1979) (also reported by Hong *et al.*, 1985) exposed male and female CD-1 mice (38/sex/group) to 0, 100, 700, or 5000 ppm 2,4-DNT in feed as described in the rat study above. Since over 70% of the mice in the highest dose group died before 12 months, these animals were not included in the analysis. Mortality among the remaining dose groups and controls ranged from 70 to 85%. Tumor incidence data were drawn from animals surviving at least 12 months. A significantly increased incidence of renal tumors was found among male mice in the 700 ppm 2,4-DNT dose group (19/28 treated vs. 0/33 control; $p = 1.32 \times 10^{-9}$, Fisher's exact test). Renal tumor types included cystic papillary adenomas, solid renal cell carcinomas, and cystic papillary carcinomas. No significantly increased tumor incidence was reported among female mice.

Ellis *et al.* (1979, 1985) treated beagle dogs (6/sex/group) with 2,4-DNT in gelatin capsules daily for 2 years at dose rates of 0, 0.2, 1.5, or 10 mg/kg body weight. The highest dose was lethal to five of the 12 treated animals. Throrough examination of all animals upon sacrifice showed no evidence of carcinogenicity of 2,4-DNT.

The Chemical Industry Institute of Toxicology (CIIT, 1982) exposed male and female F344 rats (130/sex/dose) to technical grade DNT (76% 2,4-DNT and 19% 2,6-DNT) feed such that daily dosing was 0, 3.5, 10.0, and 35.0 mg/kg-day. The entire high-dose group was sacrificed at 55 weeks due to significantly reduced survival. Twenty rats (/sex) were examined histopathologically at this time. The animals in the remaining dose groups were sacrificed at the scheduled time of 104 weeks. The incidences of hepatocellular carcinoma and neoplastic nodules of the liver are reported in Table 1. Cholangiocarcinomas were also reported in 3/20 high-dose male rats (at 55 weeks) and 2/23 mid-dose male rats (at 104 weeks).

Table 1. Tumor incidence in male and female F344 rats exposed to technical grade dinitrotoluene (DNT) in feed (CIIT, 1982).

	males (mg/kg-day)				females (mg/kg-day)			
tumor type	0	3.5	10.0	35.0*	0	3.5	10.0	35.0*
hepatocellular carcinoma	1/61	9/70	22/23	20/20	0/57	0/61	40/68	11/20
neoplastic nodules	9/61	11/70	16/23	5/20	5/57	12/61	53/68	12/20

*All the high-dose group animals were sacrificed at 55 weeks due to significantly reduced survival. Histopathological examinations were performed on 20 rats/sex.

Leonard *et al.* (1987) exposed 20 male CDF(F344)/CrlBR rats to 2,4-DNT in the diet for 12 months such that daily dose rate was 27 mg/kg-day. No evidence of carcinogenicity was found, however, the study was short in duration and the number of animals was small.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The US EPA (1980) derived a cancer potency value based on the tumor incidence data in the study by Lee *et al.* (1978) showing the induction of liver and mammary tumors in female CD rats. This study was selected over the NCI (1978) study because of published reservations by NCI concerning the adequacy of the study for estimating cancer potency in humans.

Methodology

The US EPA (1980) calculated a "transformed" dose rate of 0, 0.71, 3.9, and 34.0 mg/kg-day for the animals in the study by Lee *et al.* (1978) exposed to 0, 15 100 and 700 ppm 2,4-DNT in their diet, respectively. A linearized multistage model was fit to the combined mammary gland and liver tumor incidence data presented in Table 1 in order to calculate an animal cancer potency value (q_{animal}). The calculated q_{animal} was 0.058 $(mg/kg\text{-}day)^{-1}$. The q_{animal} was converted to a human cancer potency (q_{humna}) based on the following relationship, where bw_{animal} is the assumed body weight for the test species (Lee *et al.*, 1978; bw_{animal} = 0.464 kg) and bw_{human} is the assumed human body weight (70 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting q_{human} is 0.31 $(mg/kg\text{-}day)^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 8.9 E-5 $(\mu g/m^3)^{-1}$.

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1,4-DIOXANE

CAS No: 123-91-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From ACGIH, 1994)

Molecular weight	88.1
Boiling point	101.1°C
Melting point	11.8°C
Vapor pressure	29 mm Hg @ 20°C
Air concentration conversion	1 ppm = 3.6 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: (7.7 E-6 µg/m^3)$^{-1}$
Slope Factor: 2.7 E-2 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1989)]

III. CARCINOGENIC EFFECTS

Human Studies

The two human epidemiological studies of the potential carcinogenicity of 1,4-dioxane (Thiess *et al*. (1976); Buffler *et al*. (1978)) did not show significant changes in the incidence of carcinogenicity. However, neither study had sufficient statistical power to detect moderate changes in cancer incidence due to the small size of the sample groups or the short duration of the studies.

In the study by Thiess *et al*. (1976), 74 German workers were exposed to various concentrations of 1,4-dioxane for an average of 24.9 years. Of the 74 workers, 24 were working at the end of the follow-up period (1964 - 1974), 23 were no longer working, 15 had retired, and 12 had died. Of the 12 deaths, two were attributed to neoplastic diseases (1 lamellar epithelial carcinoma and 1 myelofibrotic leukemia). The expected number of deaths during this period in the cohort was 14.5, based on Federal Republic of Germany mortality statistics. The overall death rate and the cancer death rate were not significantly increased over controls.

Buffler *et al*. (1978) studied the mortality of 165 workers exposed to 1,4-dioxane in a dioxane-manufacturing and processing facility in Texas. The employees were exposed to dioxane for at least 1-month up to 21 years (April, 1954 to June, 1975), and were divided into two cohorts. The cohort of manufacturing workers was composed of 100 individuals, and the processing workers numbered 65. The concentrations of dioxane in the workplaces were less than 25 ppm. Seven deaths occurred in the manufacturing cohort (4.9 expected), two from neoplasms (0.9 expected). Five deaths occurred in the processing cohort (4.9 expected), one from cancer (0.8 expected). These mortality and cancer rates were not higher than the expected from Texas age- and sex-

specific death rates for 1960-1969. Due to the small sample size and short exposure period of the study, the authors concluded that the negative results were not conclusive.

Animal Studies

Male Wistar rats (n = 26) were given drinking water containing 1% dioxane for 63 weeks (Argus *et al*., 1965). A group of 9 rats given untreated water were used as controls. Six hepatomas, one kidney tumor, and one case of leukemia were found in the treated animals. One lymphosarcoma was found in the control group. The increased incidence of cancer in the treated animals was not statistically significant ($p < 0.05$). However, due to the small size of the control group, this study was of very limited sensitivity, and therefore inconclusive.

Another drinking water study in male rats was conducted by Hoch-Ligeti *et al*. (1969) and further reported on by Argus *et al*. (1973). In this study, male Charles River rats (30 per group) were given 0, 0.75, 1.0, 1.4, or 1.8% dioxane in their drinking water from 2-3 months of age for 13 months. Animals were killed 16 months following treatment or earlier if tumors in the nasal cavity were observed. Survival data was not reported. Nasal histological examinations were only performed on animals with grossly visible tumors. The incidence of tumors found in this study are presented in Table 1.

Table 1. Tumor incidence in male Charles River rats exposed to 1,4-dioxane in drinking water (Hoch-Ligeti *et al*., 1969; Argus *et al*., 1973).

	Tumor Incidence				
1,4-Dioxane Concentration (%)	0	0.75	1.0	1.4	1.8
Hepatocarcinomas	0/30	0/30	0/30	2/30	2/30
Nasal tumors	0/30	1/30	1/30	2/30	2/30
Hepatic tumors (total)	NR	4/30	8/30	16/30	25/30

NR = Not reported

Kociba *et al*. (1974) studied the effects of dioxane in the drinking water of male and female Sherman rats. Rats (60/sex/group) were exposed to 0, 0.01, 0.1, or 1.0% dioxane for 2 years. Actual dosages of dioxane were estimated using drinking water consumption and body weight data. The dosages were 0, 9, 94, or 1015 mg/kg/day for the males, and 0, 14, 148, or 1599 mg/kg/day in females. Because the tumor incidence data are averaged for the combined male and female responses, the doses were also averaged. Mortality in the combined high dose group was 45% after 1 year of exposure, compared with 12% in the control group. The tumor incidence data is summarized in Table 2.

King *et al*. (1975) exposed male and female B6C3F1 mice (50/sex/group) to dioxane in the drinking water for 40-43 weeks. Concentrations of dioxane used were 0, 0.5, or 1.0 %. No tumors were observed in any group at the end of the treatment period. According to IARC (1976), the duration of this study was insufficient to detect hepatocarcinoma, the tumor most commonly found in the National Cancer Institute (NCI, 1978) study.

Table 2. Tumor incidence in male and female Sherman rats exposed to dioxane in drinking water (Kociba *et al*., 1974).

	Tumor Incidence			
1,4-Dioxane Concentration (%)	0	0.01	0.1	1.0
Hepatocarcinomas	1/120	0/120	1/120	10/120
Nasal tumors	0/120	NR	NR	3/120

NR = Not reported

The NCI conducted a bioassay on male and female B6C3F1 mice (50/sex/group) given 0, 0.5, or 1.0% dioxane in the drinking water from 5 weeks to 90 weeks (NCI, 1978). Mortality of the male rats was only 10% in the male mice after 91 weeks. Mortality in the female mice increased with increasing dose, up to 44% in the high dose group. Tumor incidence data from this study is presented in Table 3. The incidence of hepatocarcinomas was significantly increased in both the male and female mice exposed to the low and high concentrations of dioxane, compared with controls.

Table 3. Tumor incidence in male and female B6C3F1 mice exposed to 1,4-dioxane in the drinking water (NCI, 1978).

	Tumor Incidence		
1,4-dioxane Concentration	0	0.5	1.0
Hepatocarcinomas (males)	2/49	18/50	24/47
Hepatocarcinomas (females)	0/50	12/48	29/37

In addition to the mouse study. the National Cancer Institute (1978) also exposed male and female Osborne-Mendel rats to 0, 0.1, or 1.0 % dioxane in their drinking water for 110 or 90 weeks, respectively. The incidences of nasal tumors in these groups were 0/33, 12/33, and 16/33 in the males, and 0/34, 10/35, and 8/35 in the females.

Male guinea pigs (20/group) were exposed to 0 or 0.5-2.0% dioxane in the drinking water for 23 months. After 28 months, the animals were killed and tumor incidence was recorded. Tumor incidences in the treated animals included 3 animals with hepatomas, 2 with gall bladder carcinomas, and one with adenoma of the kidney. Tumors were not found in the controls (n = 10). Although the cancer incidences were not significantly different from the controls, IARC (1976) concluded that dioxane caused liver and gall bladder tumors.

In an inhalation study, Torkelson *et al*. (1974) exposed groups of 288 male or female Wistar rats to 111 ppm 1,4-dioxane for 7 hours/day, 5 days/week, for 2 years. Control rats (192 male or female rats) were exposed to filtered room air. Weight gain among males and females was not

affected by dioxane treatment compared with controls. Survival rates were not significantly different between control and treated rats. Similarly, the tumor incidence was not significantly different with dioxane treatment. The estimated equivalent dose rate from the inhalation study was 100 mg/kg/day, based on default values for rat body weight and breathing rate. This estimated dose is much lower than that used in the drinking water studies described above.

Male and female Swiss-Webster mice (30/sex/group) were exposed dermally to an unspecified concentration of dioxane in acetone 3 times/week (King *et al*., 1975). Dioxane was tested either as a complete carcinogen for 60 weeks, or as a promoter, following a single exposure to DMBA followed by 59-week exposure to dioxane. Control mice were treated with the acetone vehicle alone or with DMBA. Dioxane was a significant promoter of skin carcinomas compared to controls treated with DMBA only. However, no significant increase in skin papillomas or carcinomas was observed in the test for complete carcinogenicity.

The tumor-intitiating properties of dioxane were investigated using the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) in Sencar mice (40 females/group) (Bull *et al*., 1986). Mice were exposed to a single oral, topical, or subcutaneous dose of 1,000 mg/kg dioxane, followed by TPA in acetone 3 times per week for up to 52 weeks. No significant increase in skin tumor incidence was reported in the mice, however, tumor incidence was not reported and length of observation was not specified.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Five studies (Argus *et al*., 1965; Hoch-Ligeti *et al*., 1969; Argus *et al*., 1973; Kociba *et al*., 1974; and NCI, 1978) allow the estimation of cancer potency values for dioxane. Of these studies, only the Kociba *et al*. (1974) and NCI (1978) studies were considered for the determination of the cancer potency factor for dioxane.

In the Argus *et al*. (1965) study, 26 adult male Wistar rats were given drinking water containing 1% dioxane for 63 weeks. The estimated dose of dioxane by the authors was 300 mg/day. The incidence of liver hepatomas (6/26) in the treated animals was significantly higher than in untreated control animals (0/9) but not significantly different from historical control animals. The cancer incidence in the treated animals is considered biologically significant, but is not quantitatively suitable for use as the basis of a cancer potency factor for dioxane.

The Hoch-Ligeti *et al*. (1969) and Argus *et al*. (1973) study failed to demonstrate significant differences in tumor incidences between treated and control rats. The trend for increasing tumors was marginally signficant ($p < 0.07$). When analyzed, these data yeild a human cancer potency factor of 2.0×10^3 to 5.8×10^3 $(mg/kg/day)^{-1}$.

In the Kociba *et al*. (1974) study, 60 male and female Sherman rats were exposed to concentrations of dioxane of 0, 0.01, 0.1, and 1.0 % for 716 days. The tumor incidence for the combined male and female data set was 1/120, 0/120, 1/120, and 10/120. Using the multistage

model and an interspecies scaling factor, an estimate for human cancer potency of dioxane was 5.7×10^{-4} $(mg/kg/day)^{-1}$. This dataset was not used since tumor incidences for males and females were averaged.

The National Cancer Institute (1978) exposed male and female Osborne-Mendel rats to 0, 0.1, or 1.0 % dioxane in their drinking water for 110 or 90 weeks, respectively. The incidence of nasal tumors were 0/33, 12/33, and 16/33 in the males, and 0/34, 10/35, and 8/35 in the females. From measured water consumption and body weight data, the human cancer potency from a multistage polynomial fit of these data was 9.5×10^{-3} $(mg/kg/day)^{-1}$ from male rat data, and 4.9×10^{-3} $(mg/kg/day)^{-1}$ from female rat data. An adjustment for early mortality following the procedure of EPA (1988) yielded cancer potencies of 1.1×10^{-2} $(mg/kg/day)^{-1}$ and 6.0×10^{-3} $(mg/kg/day)^{-1}$ from male and female rat data, respectively. The NCI (1978) study using B6C3F1 mice was used as the basis for the cancer potency for dioxane. This study contained the best data on the most sensitive species and sex, and the most sensitive target tissue. In this study, 50 male or female mice were exposed to 0, 0.5, or 1.0% dioxane for 90 weeks. Average doses were determined from weekly measurements of water consumption. The estimated doses were 0, 720, and 830 mg/kg/day for the males and 0, 380, and 860 mg/kg/day for the females. The incidence of hepatocarcinomas were 2/49, 18/50, and 24/47 for males, and 0/50, 12/48, and 29/37 for the females. The incidence of hepatocarcinomas or adenomas were 8/49, 19/50, and 28/47 in males, and 0/50, 21/48, and 35/37 in females.

Methodology

A linearized multistage model (CDHS, 1985) was fitted to the female mouse combined hepatocellular carcinoma and adenoma incidence from the NCI (1978) study. The animal cancer potencies were 8.3×10^{-4} and 1.4×10^{-3} $(mg/kg/day)^{-1}$, for the males and females, respectively. The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. The animal cancer potencies were therefore adjusted for the short duration of the experiment, using the factor $(104/90)^3$. A value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse). Body weights for interspecies scaling were assumed to be 0.04 and 0.035 kg for males and females, respectively. The combined incidence of hepatocarcinomas and adenomas in males and females gave human cancer potencies of 1.5×10^{-2}, and 2.7×10^{-2} $(mg/kg/day)^{-1}$, respectively. The combined incidence of hepatocarcinomas and adenomas in females was used to derive the human cancer potency for dioxane of 2.7×10^{-2} $(mg/kg/day)^{-1}$. The airborne unit risk factor for dioxane of 7.7 E-6 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES assuming a human body weight of 70 kg and an inhalation rate of 20 m^3/day.

V. REFERENCES

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EPICHLOROHYDRIN

CAS No: 106-89-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	92.5
Boiling point	116.5°C
Melting point	-48°C
Vapor pressure	10 mm Hg at 16.6°C
Air concentration conversion	1 ppm = 3.79 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.3 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 8.0 E-2 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

A retrospective cohort mortality study of 533 white male Dow Chemical Company employees with potential epichlorohydrin (ECH) exposure for at least 1 month between October 1957 and November 1976 was performed by Shellenberger *et al*. (1979; reviewed by US EPA, 1984). Two cancer deaths were observed; this was less than the number expected (3.5) for the entire group. However, in a review of this study, US EPA (1984) pointed out that this study is inadequate for ECH carcinogenicity evaluation because of low exposures, short exposure duration, a short study period and the very young age of the cohort.

Enterline (1978, 1981; reviewed by US EPA, 1984) conducted a retrospective cohort mortality study of epichlorohydrin workers for Shell Oil Company. The cohort consisted of 864 workers at Shell plants in Louisiana and Texas; deaths were compared by cause with expected deaths in Louisiana and Texas, respectively. Study data were analyzed by vital status as of December 31, 1977 and as of December 31, 1979 (reported by Enterline in 1978 and 1981, respectively) for the cohort exposed to ECH for at least 3 months before January 1, 1966. Overall mortality in the ECH-exposed group was not increased compared to controls; a non-statistically significant increase in respiratory cancer and leukemias was reported (standardized mortality ratios (SMRs) of 146.2 and 224.7, respectively). Additionally, the data reported in 1978 indicated an apparent increase with increasing latent period since 11 of 12 of the respiratory cancer or leukemia deaths occurred in workers 15 or more years after first exposure. The possibility existed that increasing observation time would reveal more respiratory cancer/leukemia deaths. However, the 1981 report (Enterline, 1981) including the most recent data indicated that the SMRs for both respiratory cancer and leukemia in the ECH-exposed group decreased, especially for those with greater than 15 years since first exposure. US EPA (1984) also noted that smoking was a

potential confounder, exposure analysis failed to show a dose-response trend, and exposure to multiple chemicals was also a potential confounder. The SMR for respiratory cancer was much higher in workers exposed in the isopropyl alcohol manufacturing unit to other chemicals in addition to ECH than in the group exposed to ECH alone (SMRs = 214.8 and 63.3, respectively). US EPA (1984) concluded that the studies by Enterline (1978, 1981) provide only limited evidence for the human carcinogenicity of ECH.

Tassignon *et al*. (1983) studied the mortality of workers exposed to ECH in four European manufacturing plants which produced ECH, epoxy resins, glycerin and other ECH-derived specialty chemicals. Data was collected on 606 male workers with at least one year of exposure to ECH starting at least 10 years before December 31, 1978. No excess cancer mortality due to ECH exposure was observed; however, the authors noted that the small cohort size, short duration of the observation period and the limited number of deaths due to low average age (42 years) limited the power of the study.

Animal Studies

Female ICR/Ha Swiss mice were treated with ECH by dermal application, subcutaneous injection or intraperitoneal injection (Van Duuren *et al*., 1974). Dermal applications were performed 3 times/week; 2 mg ECH in 0.1 ml acetone was applied to 50 animals for 83 weeks. Untreated and vehicle control groups of 100 and 50 animals, respectively, were included. No increased incidence in skin tumors were noted in the treated animals. Intraperitoneal injections were performed weekly for 64 weeks; 1 mg ECH in 0.05 ml tricaprylin was injected into 30 animals. Untreated and vehicle control groups of 100 and 30 animals, respectively, were included. No treatment-related tumor induction was noted in the exposed animals. Subcutaneous injections were performed weekly for 83 weeks; 1 mg ECH dissolved in 0.05 ml tricaprylin was injected into 50 animals. Untreated and vehicle control groups of 100 and 50 animals, respectively, were included. An increased incidence of injection site tumors was noted (6/50 sarcomas, 1/50 adenocarcinomas) in the treated animals as compared to controls (no tumors in untreated controls, 1/50 sarcomas in vehicle controls).

Laskin *et al.* (1980) exposed male non-inbred Sprague-Dawley rats to 10, 30 or 100 ppm ECH by inhalation for the lifetime of the animals. Exposure durations were 6 hours/day, 5 days/week. Control groups consisted of 50 untreated animals and 100 air-treated animals. All groups demonstrated a high degree of early mortality, primarily due to respiratory disease (50% mortality by 64 weeks). Of a group of animals exposed to 100 ppm ECH for 6 weeks, 18/140 developed nasal cavity tumors, which were primarily squamous cell carcinomas. A group of 100 animals exposed for life (approximately 144 weeks) to 30 ppm developed 2 respiratory tract tumors; 1 larynx squamous papilloma and 1 nasal squamous cell carcinoma. The laryngeal tumor was misidentified in the original manuscript as a nasal tumor (US EPA, 1984). These tumor incidences were not significant when compared to those of the control group; however, they were significant when compared to the 1920 historical control animals from that laboratory, none of which had developed nasal squamous carcinoma. No nasal or respiratory tract tumors were noted in a group of 100 animals exposed for life to 10 ppm. No equivalent nasal or respiratory tumors were noted in the control groups. CDHS (1988) noted that only 18%, 26%

and approximately 50% of the animals in the 30 ppm, 10 ppm and 100 ppm dose groups, respectively, survived to mean time-to-tumor observed in the 100 ppm group (86 weeks).

Konishi *et al*. (1980) exposed male Wistar rats (18/group) to epichlorohydrin in drinking water at concentrations of 0, 375, 750 or 1500 ppm for up to 81 weeks; treatment was intermittently suspended between 60 and 81 weeks for all three epichlorohydrin treatment groups due to toxicity. Total dose for the 375, 750 and 1500 ppm treatment groups was 5.0, 8.9 and 15.1 g/animal, respectively. A dose-related increase in forestomach tumor (papillomas and squamous cell carcinomas) incidence was observed. Tumor incidence data is listed in Table 1.

Table 1: Incidence of forestomach tumors in male Wistar rats exposed to epichlorohydrin in drinking water (Konishi *et al*., 1980)

Concentration (ppm)	Calculated dose[1] (mg/kg-day)	Tumor incidence	
		papillomas	squamous cell carcinomas
0	0	0/10	0/10
375	15.1	0/9	0/9
750	31.9	1/10	1/10
1500	76.1	7/12	2/10

1. As listed in CDHS (1988).

Male and female ICR/HA Swiss mice (50/sex/group) were exposed to pure (99.9%) trichlorethylene (TCE), industrial grade (99.4%) TCE, or TCE containing 0.8% ECH, 0.8% 1,2-epoxybutane, or 0.8% ECH and 0.8% 1,2-epoxybutane by gavage for 104 weeks (Henschler *et al*., 1984). Corn oil vehicle control groups were included. Initial dosing provided TCE exposures of 2400 mg/kg/day^{-1} and 1800 mg/kg/day^{-1} for male and female mice, respectively. Because of toxicity, dosing was halted for all groups during weeks 35-40, 65 and 69-78. All doses were reduced by a factor of 2 at week 40. Mortality was significantly increased compared to controls in all male treatment groups, and in female treatment groups receiving pure TCE and TCE/ECH. Significant increases in the incidence of squamous cell carcinomas of the forestomach were observed in both male and female animals exposed to TCE/ECH. The tumor incidence in animals exposed to pure TCE was comparable to control values. Tumor incidence data is listed in Table 2.

Table 2. Epichlorohydrin-induced forestomach tumor incidence in male and female Swiss mice (Henschler *et al*., 1984)

Treatment group	Tumor incidence[1]	
	males	females
vehicle controls	1/50	1/50
pure trichloroethylene	1/50	0/50
pure trichloroethylene + 0.8% epichlorohydrin	8/50	12/50

Table 2 (continued). Epichlorohydrin-induced forestomach tumor incidence in male and female Swiss mice (Henschler *et al*., 1984)

1. Papilloma and squamous cell carcinoma incidences combined.

Male and female Wistar rats (50/sex/group) were exposed to 0, 2 or 10 mg/kg body weight epichlorohydrin by gavage 5 times/week for 2 years (Wester *et al*., 1985). Intestinal obstruction by trichobezoars (hairballs) resulted in intercurrent mortality after 4 months. Cumulative incidences for control, low-dose and high-dose animals, respectively, were 8, 16 and 19 for females, and 1, 0 and 5 for males. The study diet formulation was changed at 4 months; this resulted in decreased mortality from this cause for the remainder of the study. The percentage of surviving animals after 1 and 2 years of treatment is listed in Table 3.

Table 3. Survival of male and female Wistar rats exposed to epichlorohydrin by gavage (Wester *et al*., 1985)

Dose level (mg/kg body weight)	% survival after 1 year of treatment		% survival after 2 years of treatment	
	males	females	males	females
0	98	80	76	62
2	94	62	62	40
10	90	62	58	44

Treatment-related increases in the incidence of forestomach tumors (papillomas and squamous cell carcinomas) were observed in both male and female animals. Tumor incidence data is listed in Table 4.

Table 4. Epichlorohydrin-induced forestomach tumor incidence in male and female Wistar rats (Wester *et al*., 1985)

Sex	Dose level (mg/kg body weight)	Tumor type	Tumor incidence
male	0	papilloma	1/50
	2		6/49
	10		4/49
	0	squamous cell carcinoma	0/50
	2		6/49
	10		35/49
female	0	papilloma	2/47
	2		3/44
	10		0/39
	0	squamous cell carcinoma	0/47
	2		2/44
	10		24/39

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Cancer potency values are based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that a value derived from that data set would not be appropriate (CDHS, 1985). Several studies describe ECH-induced tumor incidence data which can be used to generate a cancer potency factor (male Wistar rat forestomach papilloma and squamous cell carcinoma data, Konishi *et al*. (1980); male Sprague-Dawley rat nasal tumor data, Laskin *et al.* (1980); male and female ICR/HA Swiss mouse forestomach squamous cell carcinoma data, Henschler *et al.* (1984); male and female Wistar rat papilloma and squamous cell carcinoma data, Wester *et al.* (1985). The data from the study by Konishi *et al*. (1980) was chosen by CDHS (1988) as the basis for a cancer potency factor for ECH. Data from the Laskin *et al*. (1980) study was considered to be less suitable for generating a cancer potency factor than data from the Konishi *et al*. (1980) study because of the poor survival of the study animals. The studies by Henschler *et al.* (1984) and Wester *et al.,* (1985) contained potential confounding factors. The ECH-exposed animals in the Henschler *et al.* (1984) study were also exposed to trichloroethylene. The animals used in the Wester *et al*. (1985) study exhibited trichobezoar-induced intestinal obstructions early in the study due to the diet composition; CDHS (1988) noted that those obstructions could have been a contributing factor to the observed forestomach carcinogenesis.

Methodology

A linearized multistage model (CDHS, 1985) was fitted to male Wistar rat forestomach papilloma and carcinoma incidence data (Konishi *et al*., 1980). US EPA (1984) lists the half-life of ECH in water as 0.69 days. Assuming first order decay due to hydrolysis, this corresponds to an average concentration throughout the day of 63% of the concentration of the freshly prepared solution. The control, low, mid and high dose groups were reported to have received cumulative doses of 0, 5.0, 8.9 and 15.1 grams (Konishi *et al*., 1980); however, these data do not compensate for hydrolysis loss of ECH. CDHS (1988) estimated the actual daily exposures after hydrolysis compensation for the low, mid and high dose groups to be 15.1, 31.9 and 76.1 mg/kg-day, respectively. This assumes a body weight of 400 grams for a control Wistar rat, and utilizes the body weight data supplied by Konishi *et al*. (1980) which indicated that the low, mid and high dose animals weighed 7.7, 22.4 and 44.9% less than the controls, respectively. Upper 95% confidence bounds on carcinogenic potency (q_1^*) were estimated using the incidences of forestomach tumors in animals surviving to the end of the study (81 weeks) and the above dose estimates. Estimates of lifetime potency values (q_{animal}) were calculated from the q_1^* derived from the 81 week study using the relationship $q_{animal} = q_1^* * (104/81)^3$. Estimates for q_{animal} of 0.015 and 0.011 $(mg/kg\text{-}day)^{-1}$ were obtained for the benign squamous cell papillomas and malignant squamous cell carcinomas, respectively. The fitted dose response functions associated with these potency estimates exhibited significant upward curvature ($p = 0.03$). Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors, using the relationship ($q_{human} = q_{animal} * (bw_h / bw_a)^{1/3}$), where q_{human} is the human potency, q_{animal} is the animal potency, and bw_h and bw_a are the human and animal body weights,

respectively. Human carcinogenic potency values (q_{human}) of 0.08 and 0.06 mg/kg-day^{-1} were derived from the q_{animal} values for benign squamous cell papillomas and malignant squamous cell carcinomas, respectively. A unit risk factor was calculated by OEHHA/ATES from the benign squamous cell papilloma data-derived q_{human} value using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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ETHYLENE THIOUREA (ETU)

CAS No: 96-45-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	102.17
Boiling point	not available
Melting point	200-203 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.179 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 4.5 E-2 $(mg/kg\text{-}day)^{-1}$
[Rat thyroid tumors (Graham *et al*., 1975), contained in Gold *et al*. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of ethylene thiourea (ETU) in humans are known to exist.

Animal Studies

Male and female 7-day old $B6C3F_1$ and $B6AKRF_1$ mice (18/sex/group) were exposed to 215 mg/kg body weight ETU by gavage from 1 week of age until 4 weeks of age (Biogenics Research Labs, Inc., 1968; Innes *et al*., 1969). The animals were then fed diets containing 646 mg/kg diet ETU until the end of the experiment (82-83 weeks). Increases in liver tumors (hepatomas) were seen in males and females of both mouse strains used; an increased incidence of lymphomas was also seen in male and female $B6AKRF_1$ mice. Tumor incidence data is listed in Table 1.

Male and female Charles River CD rats (26 animals/sex/group) were fed diets containing 0, 175 or 330 ppm technical grade ETU (97% pure) for 18 months; 5 animals of each sex were then sacrificed (Ulland *et al*.,1972). The remaining animals were followed for 6 months. Increased incidences of thyroid carcinomas were noted in both males and females; thyroid carcinoma incidences were 0/26, 3/26 and 17/26 for control, low-dose and high-dose males, respectively, and 0/26, 3/26 and 8/26 for control, low-dose and high-dose females, respectively.

Table 1. Ethylene thiourea (ETU)-induced tumor incidence in (C57BL/6×C3H/Anf)F_1 and (C57BL/6×AKR)F_1 mice (Innes *et al*., 1969)

Sex/strain	Dose group	Tumor type	Tumor incidence
Male (C57BL/6×C3H/Anf)F_1	control	liver tumors	8/79
	treated		14/16
Female (C57BL/6×C3H/Anf)F_1	control	liver tumors	0/87
	treated		18/18
Male (C57BL/6×AKR)F_1	control	liver tumors	5/90
		lymphomas	1/90
	treated	liver tumors	18/18
		lymphomas	3/18
Female (C57BL/6×AKR)F_1	control	liver tumors	1/82
		lymphomas	4/82
	treated	liver tumors	9/16
		lymphomas	4/16

Graham *et al*. (1973, 1975) exposed male and female Charles River CD rats (initial group sizes 68 animals/sex/group) to diets containing ETU at levels of 5, 25, 125, 250 or 500 mg/kg diet. An untreated control group was included. Interim sacrifices were conducted at 2, 6, 12 and 18 months; the study was terminated at 24 months. An increased incidence of thyroid tumors (adenomas and carcinomas) was noted in males and females (combined). Tumor incidence data is listed in Table 2.

Table 2. Ethylene thiourea-induced thyroid tumor incidence in male and female (combined) Charles River CD rats (Graham *et al*., 1973, 1975)

Ethylene thiourea dietary level (mg/kg diet)	Average dose[1] (mg/kg-day)	Tumor incidence[2]
0	0	2/72
5	0.225	2/75
25	1.13	1/73
125	5.63	2/73
250	11.3	16/69
500	22.5	62/70

1. Doses as reported by Gold *et al*. (1984).
2. Tumor incidences as reported by Gold *et al*. (1984)

Male and female Charles River CD rats were exposed to diet containing 0, 175 or 350 mg/kg ETU for 78 weeks, then switched to control diet for an additional observation period of 26 weeks (Weisburger *et al*., 1981). A significantly increased incidence of thyroid follicular-cell carcinomas was noted in both male and female rats. Tumor incidences were 0/10, 2/26 and

15/26 in pooled control, low-dose and high-dose male rats, respectively, and 0/10, 2/26 and 6/26 in pooled control, low-dose and high-dose female rats, respectively.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The results of several studies are listed in Gold *et al.* (1984). Innes *et al*. (1969) administered ethylene thiourea (ETU) to small groups of both sexes of $B6C3F_1$ and $B6AKF_1$ mice; Graham *et al*. (1973, 1975) performed relatively large multiple dose studies in Charles River CD rats of both sexes; Weisburger *et al.* (1981) and Ulland *et al.* (1972) conducted moderately sized studies in male and female Charles River CD rats. Because all male $B6C3F_1$ and female $B6AKF_1$ mice treated with ETU developed liver tumors, an upper bound estimate on potency could not be determined for these studies. The lower bound estimates of cancer potency derived from the mouse data are consistent with potencies derived from the studies in rats. Further, cancer potencies derived from the rat studies are consistent with one another. The value selected is derived from the highest quality study, Graham (1973, 1975), which had a large sample size and used multiple dose groups. The target site chosen for the analysis was the thyroid in the Charles River CD rats, the most sensitive site (see Table 2) (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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HEXACHLOROBENZENE

CAS No: 118-74-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	284.8
Boiling point	323-326°C
Melting point	231°C
Vapor pressure	1.09 E-05 mm Hg at 20°C
Air concentration conversion	1 ppm = 11.65 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 5.1 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.8 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from potency derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

No adequate epidemiological studies of cancer in people exposed to hexachlorobenzene (HCB) are available. The only reported study found increases in porphyria, neurological, dermatological and orthopedic disorders and thyroid enlargement among 161 individuals (63 women, 98 men) studied out of a group of approximately 4000 who had suffered hexachlorobenzene poisoning 25 years previously as a result of eating HCB-treated wheat seed (Peters *et al.*, 1982, 1983). No increases in cancer incidence were reported; however, it should be noted that the methodology used in the study was not designed to evaluate excess cancer occurrence.

Animal Studies

A number of feeding studies have been conducted in hamsters, rats and mice. Hexachlorobenzene has been found to induce tumors in the liver, adrenal gland, thyroid gland, parathyroid gland, kidney, lymphoid tissue and endothelial tissue.

Cabral *et al.* (1977) fed male and female Syrian golden hamsters diets containing 0, 50, 100 or 200 mg/kg diet HCB for the life of the animals. Treatment group sizes for the control, low-dose, mid-dose and high-dose groups were 40, 30, 30 and 59, respectively, for males and 40,30,30 and 60, respectively, for females. Treatment-related increases in the incidence of liver tumors (hepatomas, hemangioendotheliomas) and thyroid adenomas were observed in both males and females. Tumor incidence data is listed in Table 1.

Table 1. Hexachlorobenzene-induced tumor incidence in male and female Syrian golden hamsters (Cabral *et al.*, 1977)

Dietary HCB concentration (mg/kg diet)	Calculated daily intake (mg/kg-day)	Tumor type	Tumor incidence	
			males	females
0	0	hepatomas	0/40	0/39
50	4		14/30	14/30
100	8		26/30	17/30
200	16		49/57	51/60
0	0	hemangioendotheliomas	0/40	0/39
50	4		1/30	0/30
100	8		6/30	2/30
200	16		20/57	7/60
0	0	thyroid adenomas	0/40	0/39
50	4		0/30	2/30
100	8		1/30	1/30
200	16		8/57	3/60

Outbred Swiss mice were fed diets containing 0, 50, 100, or 200 mg/kg hexachlorobenzene for 101-120 weeks; all surviving animals were killed at 120 weeks (Cabral *et al.*, 1979). Initial group sizes were 50 animals/sex for the control and 200 mg/kg diet groups, and 30/sex for the 50, 100 and 300 mg/kg diet groups. A dose-response related increase in the incidence of liver tumors (unspecified histological type) was noted in both male and female animals. An increased incidence of liver tumors was also found in a group of 30 males and 30 females fed diet containing 300 mg/kg diet HCB for 15 weeks followed by observation until 120 weeks. Tumor incidence data is listed in Table 2.

Table 2. Hexachlorobenzene-induced liver tumors in male and female Swiss mice (Cabral *et al.*, 1979)

Dose group (mg/kg diet)	Tumor incidence	
	males	females
0	0/47	0/49
50	0/30	0/30
100	3/29	3/30
200	7/44	14/41
300 (15 weeks exposure)	1/16	1/26

Smith and Cabral (1980) exposed female Agus and Wistar rats to diets containing 100 mg/kg HCB for up to 90 or 75 weeks, respectively. An increased incidence of liver tumors (histological

type not specified) due to HCB exposure was observed in both Agus and Wistar rats; tumor incidence was 14/14 and 4/6, respectively, compared to 0/12 and 0/4, respectively, in the control animals.

Male and female Syrian golden hamsters were exposed to diet containing 0, 200 or 400 mg/kg diet HCB for 90 days; 25-50 animals/group were sacrificed on the 91st day (Lambrecht *et al.*, 1982). The remaining 25 animals/group were placed on control diet and sacrificed at 6 week intervals up to 1 year. Hepatoma incidence in the 200 and 400 mg/kg diet groups was 1/13 and 1/20, respectively, for males and 1/15 and 1/7, respectively for females. No hepatomas were noted in 43-50 control animals for each sex.

Male and female Sprague-Dawley rats (94/sex/group) were fed diets containing 0, 75 or 150 mg/kg diet HCB for up to 2 years (Lambrecht *et al.*, 1983a, b, 1986). Four animals/sex/group were killed at 0, 1,2,3,4,8,16,32 and 64 weeks. Treatment-related increases in the incidence of hepatic tumors (hepatomas, hemangiomas, hepatocarcinomas and bile duct adenomas/carcinomas) and renal-cell adenomas were noted in both male and female animals. Tumor incidence data is noted in Table 3.

Table 3. Hexachlorobenzene-induced hepatic tumors in male and female Sprague-Dawley rats (Lambrecht *et al.*, 1983 a,b; 1986)

Dose group (mg/kg diet)	Tumor type	Tumor incidence	
		males	females
0	hepatoma/hemangioma	0/54	0/52
75		10/52	23/56
150		11/56	35/55
0	hepatocarcinoma	0/54	0/52
75		3/52	36/56
150		4/56	48/55
0	bile duct adenoma/carcinoma	0/54	1/52
75		2/52	19/56
150		2/56	29/55
0	renal-cell adenomas	7/54	1/52
75		41/52	7/56
150		42/56	15/55

Arnold *et al.* (1985) conducted two studies on the effects of chronic feeding of HCB in Sprague-Dawley rats. In the first study, male and female Sprague-Dawley rats were fed diets containing 0, 0.32, 1.6, 8 or 40 mg/kg diet HCB for 3 months after weaning. Group sizes were 40/sex except for the control and high-dose groups (64 and 66/sex, respectively). After 3 months, the F_0 rats were bred and 50 pups (F_1) of each sex were randomly selected from each group. The F_1 generation animals were fed their parent's diet from weaning for their lifetime (130 weeks). A significant positive trend was noted in the incidence of parathyroid adenomas in males ($p <$

0.01); the incidence in high-dose males was also significantly greater than controls ($p < 0.05$). A significant positive trend was also noted in the incidence of adrenal pheochromocytomas in both males and females ($p < 0.05$ and $p < 0.01$, respectively); the incidence in high-dose females was also significantly greater than controls ($p < 0.01$). Tumor incidence data is listed in Table 4.

Table 4. Hexachlorobenzene-induced tumor incidence in the male and female exposed F_1 progeny of exposed F_0 Sprague-Dawley rats (Arnold *et al.*, 1985)

Dose group (mg/kg diet HCB)	Average dose[1]	Tumor type	Tumor incidence	
			males	females
0	0	parathyroid adenomas	2/48	
0.32	0.01		4/48	
1.6	0.07		2/48	
8	0.35		1/49	
40	1.72		12/49	
0	0	adrenal pheochromocytomas	10/48	2/49
0.32	0.01		12/48	4/49
1.6	0.07		7/48	4/50
8	0.35		13/49	5/49
40	1.72		17/49	17/49

1. As reported by CDHS (1988)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results from the following 3 studies provide the basis for cancer potency derivation. Cabral *et al.* (1977) treated groups of male and female Syrian golden hamsters with hexachlorobenzene in feed over the lifetime of the animals. Significant dose-related increases in hepatomas were observed in both sexes (see Table 1). Lambrecht *et al.* (1983a, b; 1986) exposed male and female Sprague-Dawley rats to hexachlorobenzene in feed for 2 years. Treated male and female rats exhibited significant increases in the incidence of hepatomas and renal-cell adenomas. Female rats also demonstrated significant increases in the incidence of hepatocellular carcinomas. No hepatocellular carcinomas were noted in control animals (see Table 3). Arnold *et al.* (1985) also observed a significant dose related increase in the occurrence of adrenal pheochromocytomas in the male and female and parathyroid adenomas in the male exposed F_1 progeny of exposed F_0 Sprague-Dawley rats (see Table 4).

Methodology

Cancer potency values are based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that the value derived from that data set is not appropriate (CDHS, 1985). For hexachlorobenzene, similar cancer potencies were derived using data from several tumor sites in different test species. Cancer potency factors (q_1^*) were derived by fitting a linearized multistage model (CDHS, 1985) to the dose-response data for induction of hepatomas in male Syrian golden hamsters (Cabral *et al.*, 1977), and hepatocellular carcinomas (Lambrecht *et al.*, 1983a, b) and pheochromocytomas (Lambrecht *et al.*, 1983a, b; Arnold *et al*., 1985) in female Sprague-Dawley rats. Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors. Assumed body weight values used for humans, hamsters and mice were 70 kg, 0.1 kg and 0.035 kg, respectively (CDHS, 1988). Lambrecht *et al.* (1983a, b) reported average body weights of 0.265 kg for female Sprague-Dawley rats; unpublished data cited by US EPA (1985) indicates that average body weights of female Sprague-Dawley rats in the study by Arnold *et al.* (1985) were 0.353 kg. A human cancer potency value (q_{human}) of 1.7 $(mg/kg\text{-}day)^{-1}$ was calculated from the male hamster hepatoma incidence data (Cabral *et al.*, 1977) and the female rat hepatocellular carcinoma incidence data (Lambrecht *et al.*, 1983a, b). A human cancer potency value of 1.8 $(mg/kg\text{-}day)^{-1}$ were calculated from female rat pheochromocytomas incidence data (Lambrecht *et al.*, 1983a, b; Arnold *et al.*, 1985). On the basis of the results stated above, a cancer potency of 1.8 $(mg/kg\text{-}day)^{-1}$ was selected for hexachlorobenzene (CDHS, 1988). The unit risk factor was derived by OEHHA/ATES from the low dose exposure cancer potency value using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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HEXACHLOROCYCLOHEXANE (TECHNICAL GRADE)

CAS No: 608-73-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	290.9
Boiling point	288°C (α-HCH); 323.4°C (γ-HCH)
Melting point	158°C (α-HCH); 113°C (γ-HCH)
Vapor pressure	0.02 mm Hg @ 20°C (α-HCH)
Air concentration conversion	1 ppm = 11.9 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 4.0 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III. CARCINOGENIC EFFECTS

Human Studies

The International Agency for Research on Cancer (IARC) concluded in 1987 that the evidence for carcinogenicity of hexachlorocyclohexane (HCH; all isomers) was inadequate in humans. However, U.S.EPA (1988) designated α-HCH and technical grade HCH as B2 (probable human) carcinogens. Several case reports suggest an association between HCH isomers, including β- and γ-HCH, and exposure and leukemia, aplastic anemia, liver cancer, soft-tissue sarcomas, and lung cancer (IARC, 1987). In all of these case reports, the exposures are not well documented. In addition, exposures to other chemicals, including some pesticides, probably occurred in these cases.

Animal Studies

The incidence of liver tumors in male and female mice has been shown to be increased in two studies of technical HCH (Kashyap *et al*., 1979; Hanada *et al*., 1973). Hanada *et al*. (1973) exposed male and female dd mice (10-11 per group; 14 controls) to 100, 300, or 600 mg/kg diet of α-, β-, γ-, or technical HCH for 32 weeks, followed by a 6-week period without chemical exposure. The incidence of hepatomas was significantly increased in animals treated with increasing doses of α-, or technical HCH (Table 1).

Table 1. Liver hepatoma incidence in dd mice treated with hexachlorocyclohexane (HCH) (Hanada *et al*. (1973).

HCH Isomer	Sex	Hepatoma incidence mg/kg diet HCH		
		100	300	600
α-HCH	males	1/8	7/7	7/7
	females	0/8	2/3	6/8
β-HCH	males	0/9	0/8	0/8
	females	0/9	0/8	0/4
γ-HCH	males	0/10	0/9	3/4
	females	0/8	0/7	1/3
Technical HCH	males	0/10	4/4	4/4
	females	0/8	3/5	5/5

In the study by Kashyap *et al*. (1979), Swiss mice (30/sex/group) were exposed to 0 or 100 mg/kg diet for 80 weeks. Mice were also exposed to technical HCH by gavage (10 mg/kg/day) or skin painting (0.25 mg in 0.1 mg olive oil). A significant increase in liver hepatocarcinomas and lymphoreticular tumors of type B was observed in mice exposed to technical HCH in the diet or by gavage (Table 2).

Table 2. Tumor incidence in mice treated with technical hexachlorocyclohexane (HCH) (Kashyap *et al*., 1979).

HCH Treatment Group	Sex	Animals/ group	Liver tumors	Total tumors
Control	m	25	4	9
	f	26	1	5
100 mg/kg/day (diet)	m	23	16	22
	f	25	9	21
10 mg/kg/day (gavage)	m	26	12	17
	f	28	7	16
0.25 mg/0.1 mg (olive oil) (gavage)	m	25	5	11
	f	18	3	7

m = male, f = female

Wolff *et al*. (1987) reported on the carcinogenic effects of γ-HCH in several strains of mice. Female yellow, black, and pseudoagouti mice (36-96 per group) were exposed to 0 or 160 ppm γ-HCH in the diet for up to 24 months. Different response rates were observed between strains, indicating significant genetic variability in response to γ-HCH. In yellow mice, a significant increase in the incidence of Clara cell hyperplasia, papillary lung tumors and hepatocarcinomas and adenomas was observed (Table 3). The higher incidence of tumors in the obese yellow mice indicate that bioaccumulation of γ-HCH in obese animals may influence carcinogenicity. Similar experiments were not done using technical HCH.

Table 3. Tumor incidence in yellow mice exposed to γ-HCH (Lindane) (Wolff *et al*., 1987)

Concentration of γ-HCH (ppm)	Lung Tumors	Liver Adenomas
0	4/95	8/93
160	18/95	33/94

Thorpe and Walker (1973) showed an increase in liver tumors of male CF1 mice fed 400 ppm γ-HCH for 110 weeks, compared with controls. The time-weighted dose was estimated as 52 mg/kg/day by US EPA (1988). In this experiment, control mice exhibited an incidence of 11/45 for liver tumors, compared to 27/29 for the 52 mg/kg/day group.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The studies by Hanada *et al*. (1973) and Kashyap *et al*. (1979) both show a carcinogenic effect on the liver in mice. The study by Nagasaki *et al*. (1975) also showed a positive carcinogenic effect in mice, but these data were considered less reliable since the tumor incidence was zero in all but the highest dose group, where it was 100%. In addition, the study by Kashyap *et al*. (1979) was among those of the longest duration available for HCH (80 weeks). The potency values from the Kashyap *et al*. (1979) and Hanada *et al*. (1973) studies are the same for liver tumors in mice. Therefore, these studies were used by CDHS (1988) to determine the cancer potency for HCH.

Methodology

A linearized multistage model was used to estimate the cancer potency of technical HCH from the Kashyap *et al*. (1979) and Hanada *et al*. (1973) data in male Swiss mice (Crump *et al*., 1982). The concentrations of technical HCH given in the feed were 0 or 100 mg/kg diet (Kashyap *et al*., 1979), and 0, 100, 300, or 600 mg/kg diet (Hanada *et al*., 1973). The tumor incidence data are shown in Tables 1 and 2 above. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value for HCH.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. The default lifespan for mice is 104 weeks. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 4.0 $[mg/kg \times day]^{-1}$ was derived (CDHS, 1988). An airborne unit risk factor of 1.1E-3 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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HYDRAZINE

CAS No: 302-01-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	32.05
Boiling point	113.5°C
Melting point	2.0°C
Vapor pressure	14.44 mm Hg @ 25°C
Air concentration conversion	1 ppm = 1.31 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.9 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 1.7 E+1 $(mg/kg\text{-}day)^{-1}$
[Calculated by US EPA (1991) from the male rat nasal cavity tumor data of MacEwan *et* al. (1980) using a linearized multistage model (Global 82), extra risk]

III. CARCINOGENIC EFFECTS

Human Studies

A published letter (Roe, 1978) presented mortality data from two hydrazine manufacturing plants (belonging to one of nine companies in the trade). This study included 423 workers employed at one plant between 1963 and 1975 (151 workers) and at a second plant (272 workers) between 1945 and 1970. Five cancer deaths were reported (three of the stomach, one prostatic and one neurogenic). A follow-up study of this cohort extended the observation period to 1982 (Wald *et al*., 1984). The only excess cancer mortality was the result of two lung cancer cases in the highest exposure group (relative risk = 1.2, 95% confidence interval 0.2 - 4.5). The author concluded that neither group of workers demonstrated an increased risk of cancer associated with occupational exposure to hydrazine. No other studies on human hydrazine exposure have been published.

Animal Studies

Several studies have tested the ability of hydrazine sulfate administered by gavage or in drinking water to induce cancer. Lung adenomas and adenocarcinomas and liver hepatomas and hepatocarcinomas were observed in both mice and rats. These studies have been reviewed by IARC (1974) and US EPA (1988). Lung tumors, reticulum-cell sarcomas and myeloid leukemias have also been observed to occur in mice exposed to hydrazine by intraperitoneal injection (Juhász *et al*., 1966; Kelly *et al*., 1969; Mirvish *et al*., 1969). MacEwan *et al*. (1981) reported that inhalation exposure to hydrazine induced lung adenomas in mice, nasal cavity tumors and thyroid adenocarcinomas in rats and nasal polyps in hamsters.

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

MacEwan *et al*. (1981) exposed C57BL/6 mice, F344 rats, Syrian golden hamsters and beagle dogs to hydrazine vapor (97% pure) by inhalation for 6 hours/day, 5 days/week for 1 year followed by a variable observation period (12-38 months). Exposure levels were 0.05, 0.25 and 1.0 ppm for mice, 0.05, 0.25, 1.0 and 5.0 ppm for rats, 0.25, 1.0 and 5.0 ppm for hamsters and 0.25 and 1.0 ppm for dogs. Lung adenomas were reported in 12/379 female mice ($p < 0.05$) exposed to 1.0 ppm hydrazine. Male and female rats demonstrated nasal cavity tumors after exposure to 1.0 ppm (11/98 and 4/97, respectively) and 5.0 ppm (72/99 and 36/98, respectively). Male rats also developed thyroid adenocarcinomas (13/99) after exposure to 5.0 ppm hydrazine. Nasal polyps were induced in male hamsters exposed to 5.0 ppm hydrazine (16/160, $p < 0.01$). No significant tumor increase was seen in either dog exposure group. This study was selected as the basis of a cancer potency factor for exposure to hydrazine by inhalation because it demonstrated a dose response, used a relevant exposure route and used hydrazine vapor instead of hydrazine sulfate.

Methodology

A linearized multistage model (Global 82) was used to calculate a slope factor of 1.7 E+1 $(mg/kg/day)^{-1}$ from the male F344 rat nasal cavity adenoma and adenocarcinoma incidence data of MacEwan *et al*. (1980). Male F344 rats were the most sensitive species and sex to the carcinogenic effects of inhaled hydrazine. Administered doses were 1.0 and 5.0 ppm; human equivalent doses were 0.01 and 0.05 mg/kg/day. Human equivalent doses were calculated on the basis of a 365 day treatment and an experimental period of 910 days. Rat body weight was assumed to be 350 g, and the animal lifespan was assumed to be 910 days. Calculation of the unit risk from the slope factor assumed a body weight of 70 kg and an inspiration rate of 20 m^3/day. EPA has stated that the unit risk should not be used if the air concentration exceeds 2 $\mu g/m^3$, since above this concentration the unit risk may not be appropriate.

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LINDANE (γ-HEXACHLOROCYCLOHEXANE)

CAS No: 58-89-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	290.9
Boiling point	323.4°C
Melting point	113°C
Vapor pressure	9.4E-6 mm Hg @ 20°C
Air concentration conversion	1 ppm = 11.9 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.1E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.1 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor reported by US EPA (1987)]

III. CARCINOGENIC EFFECTS

Human Studies

The International Agency for Research on Cancer (IARC) concluded in 1987 that the evidence for carcinogenicity of hexachlorocyclohexane (HCH; all isomers) was inadequate in humans. Several case reports suggest an association between lindane exposure and leukemia, aplastic anemia, liver cancer, soft-tissue sarcomas, and lung cancer (IARC, 1987). In all of these case reports, the exposures are not well documented. In addition, exposures to other chemicals, including some pesticides, probably occurred in these cases.

Animal Studies

Wolff *et al*. (1987) reported on the carcinogenic effects of lindane in several strains of mice. Female yellow, black, and pseudoagouti mice (36-96 per group) were exposed to 0 or 160 ppm lindane in the diet for up to 24 months. Different response rates were observed between strains, indicating significant genetic variability in response to lindane. In yellow mice, a significant increase in the incidence of lung and liver tumors was observed (Table 1). The higher incidence of tumors in the obese yellow mice indicate that bioaccumulation of lindane in obese animals may influence carcinogenicity.

Table 1. Tumor incidence in yellow mice exposed to γ-HCH (lindane) (Wolff *et al*., 1987)

Dietary Concentration of γ-HCH (ppm)	Tumor Type and Incidence	
	Lung Carcinomas	Liver Adenomas
0	4/95	8/93
160	18/95	33/94

Thorpe and Walker (1973) showed an increase in liver tumors of male CF1 mice fed 400 ppm lindane for 110 weeks, compared with controls. The time-weighted dose was estimated as 52 mg/kg/day by US EPA (1988). In this experiment, control mice exhibited an incidence of 11/45 for liver tumors, compared to 27/29 for the 52 mg/kg/day group.

A study by Goto *et al*. (1972) showed a positive effect of lindane on cancer in mice. However, this experiment used only 10 animals per treatment group and was of a short duration. The NCI (1977) study on male mice showed a significant increase in cancer incidence in mice exposed to 80, but not 160 ppm γ-HCH. The absence of a clear dose-response precluded this data from use in determining the cancer potency for lindane.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The US EPA (1988) selected the study by Thorpe and Walker (1973) as the basis for the cancer potency for lindane. This was considered to be the best study for development of a cancer potency factor for lindane because of the large sample size of mice surviving for a full lifespan, and the large numbers of tumors in the treatment group. Thorpe and Walker (1973) showed an increase in liver tumors in male CF1 mice fed 400 ppm lindane in the diet for 110 weeks, compared with controls. Control mice exhibited an incidence of 11/45 for liver tumors, compared to 27/29 for the lindane-treated group ($p < 0.01$). Some lung metastases were also reported in the male and female mice treated with lindane.

Methodology

A linearized multistage model was used to estimate the cancer potency of lindane from the Thorpe and Walker (1973) data in male CF1 mice (Crump *et al*., 1982). The concentrations of lindane given in the feed were 0 or 160 ppm. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value for lindane.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 1.1 [mg/kg x day]$^{-1}$ was reported (US EPA, 1987). An airborne unit risk factor of 3.1E-4 ($\mu g/m^3$)$^{-1}$ was calculated from the q_{human} value by OEHHA/ATES using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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4, 4'-METHYLENE BIS(2-CHLOROANILINE) (MOCA)

CAS No: 101-14-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	267.15
Boiling point	not available
Melting point	110°C
Vapor pressure	1.3×10^{-5} mm Hg at 60°C
Air concentration conversion	1 ppm = 10.9 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.3 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.5 E+0 $(mg/kg\text{-}day)^{-1}$
[Female beagle dog urinary bladder tumor data (Stula *et al*., 1977) , contained in Gold *et al*. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

IARC (1993) has reviewed several descriptive studies on the potential carcinogenic effects of 4, 4'-methylene bis(2-chloroaniline) (MOCA) in humans. An epidemiological study by Ward *et al*. (1990) examined cancer incidence in workers employed at a chemical plant in Michigan where MOCA was produced between 1968 and 1979. All 532 workers employed in 1968-79 and an additional 20 workers employed in 1980-81 who had possible exposure due to plant site contamination were included. Median duration of employment was 3.2 months. Quantitative exposure was not available; however, worker exposure may have been substantial, since worker urinary levels of MOCA several months after the end of production ranged up to 50,000 µg/l. Telephone interviews were conducted with 452 workers, and 385 participated in a urine screening examination. Three asymptomatic bladder tumors were identified. The screening procedure was supplemented for some workers with cytoscopy after a 28-year old worker was found to have a non-invasive papillary transitional-cell tumor. Low-grade papillary transitional cell carcinoma was diagnosed in 2 of 200 examined workers; one was less than 30 years old. Mean interval time from first exposure to study initiation was 11.5 years, while the latency period for most bladder carcinogens is about 20 years (Ward *et al*., 1990). This finding increases the concern that MOCA is a human bladder carcinogen, since bladder carcinoma in young men is very uncommon. A limitation of this study was that expected numbers of bladder tumors could not be calculated, as no data exists on the incidence of bladder tumors diagnosed by cytoscopy in an asymptomatic nonexposed population.

Animal Studies

Male and female HaM/ICR mice and male Charles River CD-1 rats (25/sex/species/group) were exposed to MOCA hydrochloride in the diet for 18 months by Russfield *et al*. (1975). Mice were fed diet containing 0, 1000 or 2000 mg/kg diet MOCA hydrochloride; rats were fed diet containing 0, 500 or 1000 mg/kg diet MOCA hydrochloride. Surviving animals were killed after 24 months; about 55% of the control and treated animals were still alive at 20-22 months. Hemangiomas or hemangiosarcomas were noted in 0/10 control, 3/13 low dose and 8/20 high dose male mice; hepatomas were noted in 0/20 control, 9/21 low dose and 7/14 high dose female mice ($p < 0.01$, Fisher exact test), and in 0/22 control, 1/22 low dose and 4/19 high dose rats ($p < 0.05$, Cochran-Armitage trend test).

Male and female Charles River CD rats (50/sex/group) were fed diet containing 0 or 1000 mg/kg diet MOCA in a standard diet (23% protein) for life (Stula *et al*., 1975). Average experiment duration was 80 weeks for treated and control males, 89 weeks for female controls and 78 weeks for treated females. Six animals from each group were killed for an interim evaluation at one year. Lung carcinomas were observed in 21/44 treated males ($p < 0.05$, χ^2 test) and in 27/44 treated females ($p < 0.05$, χ^2 test); a lung squamous-cell carcinomas was also observed in one treated male and female. Pleural mesotheliomas occurred in 4/44 treated males and 2/44 treated females. Hepatocellular adenomas and carcinomas occurred in 3/44 and 3/44 treated males and 2/44 and 3/44 treated females, respectively. No lung tumors, pleural mesotheliomas or hepatocellular adenomas and carcinomas were noted in control animals.

Male Charles River CD rats were fed a "protein-adequate" diet containing 0, 250, 500 or 1000 mg/kg diet MOCA (group sizes 100, 100, 75 and 50, respectively) for 18 months followed by a 32 week observation period (Kommineni *et al*., 1979). MOCA exposure was associated with decreased survival; mean survival time was 89, 87, 80 and 65 weeks for controls, low-dose, mid-dose and high-dose animals, respectively. Dose-related increases in the incidences of lung tumors, mammary adenocarcinomas, Zymbal gland adenocarcinomas and hepatocellular carcinomas were noted. Tumor incidence data is listed in Table 1.

Table 1. 4, 4'-methylene bis(2-chloroaniline) (MOCA)-induced tumor incidence in male Charles River CD rats (Kommineni *et al*., 1979)

Tumor type	dietary MOCA (mg/kg diet)			
	0	250	500	1000
lung tumors	1/100	23/100	28/75	35/50
Zymbal gland carcinomas	1/100	8/100	5/75	11/50
mammary adenocarcinomas	1/100	5/100	8/75	14/50
hepatocellular carcinomas	0/100	3/100	3/75	18/50

Stula *et al*. (1977) exposed a group of 6 female beagle dogs to a daily dose of 100 mg MOCA by capsule 3 days/week for 6 weeks, then 5 days/week for up to 9 years. A second group of 6 females served as untreated controls. One treated dog died at 3.4 years of age because of an

infection. The other animals were killed at 8.3-9 years. Transitional-cell carcinomas of the urinary bladder occurred in 4 of 5 treated dogs ($p < 0.025$, Fisher exact test), and a composite tumor (transitional-cell carcinoma/adenocarcinoma) of the urethra was noted in one dog. No urinary tract tumors were noted in the untreated controls. Tumor incidence data is listed in Table 2.

Table 2. 4, 4'-Methylene bis(2-chloroaniline) (MOCA) -induced urinary bladder tumor incidence in female beagle dogs (Stula *et al*., 1977)

Average Dose[1] (mg/kg-day)	Tumor Incidence[2]
0	0/6
7.31	4/5

1. Doses as reported by Gold *et al*. (1984).
2. Tumor incidences as reported by Gold *et al*. (1984)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results from a number of studies using Charles River CD and Wistar rats, as well as female beagle dogs, are listed in Gold *et al*. (1984). 4, 4'-Methylene bis(2-chloroaniline) induced papillary transitional cell carcinomas of the urinary bladder in dogs, whereas the liver was the most common target site in the rat studies. Dogs are more sensitive to the carcinogenic effects of the compound than rats. The compound is similar in structure to benzidine, a human bladder carcinogen, which appears to be significantly more potent in humans than rodents. Results from the Stula *et al*. (1977) dog study are used as the basis of potency estimation, despite the small numbers of animals used, because dogs may be better predictors of human carcinogenicity of this compound than rodents (Cal/EPA, 1992). Dose-response data are listed in Table 2.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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Hazardous Substance Data Bank (HSDB) 1994. National Library of Medicine, Bethesda MD (CD-ROM Version). Micromedix, Inc., Denver CO, Edition 22.

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4, 4'-METHYLENEDIANILINE

CAS No: 101-77-9

4, 4'-METHYLENEDIANILINE DIHYDROCHLORIDE

CAS No: 13552-44-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

4, 4'-Methylenedianiline

Molecular weight	198.26
Boiling point	398-399 °C at 768 mm Hg
Melting point	91.5-92 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 8.109 mg/m^3

4, 4'-Methylenedianiline didihydrochloride

Molecular weight	271.21
Boiling point	not available
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 11.09 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.6 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.6 E+0 $(mg/kg\text{-}day)^{-1}$
[Male mouse liver tumors (NTP, 1983), contained in Gold *et al*. (1987) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 4,4' methylenedianiline in humans are known to exist.

Animal Studies

Griswold *et al*. (1968) exposed a group of 20 female Sprague-Dawley rats to 30 mg 4,4' methylenedianiline dihydrochloride in 1 ml sesame oil by gavage every third day for 30 days (total dose, 300 mg/rat). The animals were then observed for a further 9 months. A group of 140 female Sprague-Dawley rats served as a negative control group. No treatment-related increase in tumor incidence was noted; however, the study duration was short, a small number of animals

was used, only one sex was used, and the primary aim of the study was to develop methods of detecting carcinogens inducing mammary tumors.

The potential carcinogenicity of 4,4' methylenedianiline dihydrochloride was studied using Fischer 344 (F344) rats and $B6C3F_1$ mice (50 animals/sex/species/group) (NTP, 1983). Animals were exposed to 150 mg/l or 300 mg/l 4,4' methylenedianiline dihydrochloride in drinking water for 103 weeks followed by one week without treatment. Untreated control groups were included. A significantly increased incidence of thyroid follicular-cell adenomas was observed in male and female mice and rats. Significantly increased incidences of hepatocellular adenomas and carcinomas were observed in female and male mice; increased incidences of neoplastic nodules were observed in male rats. Tumor incidence data is listed in Table 1.

Table 1 4,4' methylenedianiline dihydrochloride-induced tumor incidences in male and female F344 rats and $B6C3F_1$ mice (NTP, 1983; Weisburger *et al*., 1984)

Sex/species	Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
male mice	control	0	thyroid tumors	0/50
	low dose	24.5		3/50
	high dose	49.5		16/50
	control		liver tumors	17/50
	low dose			43/50
	high dose			37/50
female mice	control	0	thyroid tumors	0/50
	low dose	29.4		1/50
	high dose	59.1		15/50
	control		liver tumors	4/50
	low dose			15/50
	high dose			23/50
male rats	control	0	thyroid tumors	1/50
	low dose	7.36		4/50
	high dose	14.7		10/50
	control		hepatic neoplastic nodules	1/50
	low dose			12/50
	high dose			25/50
female rats	control	0	thyroid tumors	0/50
	low dose	8.41		5/50
	high dose	16.7		22/50

1. Doses as reported by Gold *et al*. (1987).
2. Tumor incidences as reported by Gold *et al*. (1987).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

4, 4'-Methylenedianiline

The potency for this compound was derived from the potency for the dihydrochloride using a molecular weight conversion:

$$q_h \text{ (anhydrous)} = q_h \text{ (hydrate)} \times \frac{\text{MW (hydrate)}}{\text{MW (anhydrous)}}$$

where q_h is the human potency and MW is the molecular weight. This conversion assumes that the intake of equivalent moles of the two forms of the chemical (e.g. the anhydrous and hydrate forms) results in equivalent concentrations of the active species *in vivo*.

4, 4'-Methylenedianiline didihydrochloride

Results are listed for the drinking water studies by NTP (1983) in male and female $B6C3F_1$ mice and F344 rats. Significant increases in tumors of the liver or thyroid or both are observed for all sex/species combinations tested, with male mice the most sensitive. The cancer potency listed is based on the combined incidence of benign and malignant liver tumors in male mice (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Analysis of the data set using the computer program TOX_RISK (Crump et al., 1991) indicated that inclusion of the high dose group resulted in a *p*-value of ≥ 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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MICHLER'S KETONE (4,4′-bis(dimethylamino) benzophenone)

CAS No: 90-94-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	268.35
Boiling point	>360 °C (with decomposition)
Melting point	172 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 10.98 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.5 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 8.6 E-1 $(mg/kg\text{-}day)^{-1}$
[Female rat liver tumor data (NCI, 1979), contained in Gold *et* al. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of Michler's ketone in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and $B6C3F_1$ mice were fed diets containing Michler's ketone (NCI, 1979). Mice were fed diets containing 1250 or 2500 mg/kg diet Michler's ketone for 78 weeks; animals were then maintained on control diet for an additional 13 weeks. Rats were fed diets containing 250 or 500 mg/kg diet Michler's ketone for males, 500 or 1000 mg/kg diet for females; the treatment period for both sexes was 78 weeks. The treatment period was followed by an observation period; 28 weeks for male rats and high dose female rats and 29 weeks for low dose female rats. Treatment group sizes were 50 animals/sex/species/group; control group sizes were 20 animals/sex/species.

Significant dose-related increases in incidences of liver tumors (hepatocellular adenomas and carcinomas) were observed in rats and female mice, and of hemangiosarcomas in male mice. Tumor incidence data is listed in Table 1.

Table 1. Michler's ketone-induced tumor incidence in male and female F344 rats and $B6C3F_1$ mice (NCI, 1979)

Sex/species	Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
Male mice	control	0	hemangiosarcomas	0/20
	low dose	128		5/50
	high dose	257		20/50
Female mice	control	0	liver tumors	0/20
	low dose	139		41/50
	high dose	278		49/50
Male rats	control	0	liver tumors	0/20
	low dose	7.4		17/50
	high dose	14.4		43/50
Female rats	control	0	liver tumors	0/20
	low dose	18		46/50
	high dose	37		48/50

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al.* (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The results from feeding studies by NCI (1979) are listed by Gold *et al*. (1984). Rats are more sensitive than mice to induction of tumors due to exposure to Michler's ketone, with male and female rats having similar sensitivity. The cancer potency factor for Michler's ketone was derived from dose-response data for liver tumors in female rats as listed in Table 1 (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

California Environmental Protection Agency (Cal/EPA) 1992. Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens. Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section, Berkeley, CA.

Gold, L., Sawyer, C., Magaw, R., Backman, G., de Veciana, M., Levinson, R., Hooper, N., Havender, W., Bernstein, L., Peto, R., Pike, M., and Ames, B. 1984. A Carcinogenic Potency Database of the standardized results of animal bioassays. Environ. Health Perspect. 58:9-319.

Hazardous Substance Data Bank (HSDB) 1994. National Library of Medicine, Bethesda MD (CD-ROM Version). Micromedix, Inc., Denver CO, Edition 22.

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N-NITROSO-N-DIBUTYLAMINE

CAS No: 424-16-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	158.2
Boiling point	116° C @ 14 mm Hg
Melting point	0.5° C
Vapor pressure	Not found
Air concentration conversion	1 ppm = 6.46 mg/m^3 @ 25° C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.0 E-2 $(\mu g/m^3)^{-1}$
Slope Factor: 3.1 E-3 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There is no direct evidence that links nitrosamines, including N-Nitroso-N-dibutylamine (NDBA), to human cancer. The US EPA (1980) and IARC (1978) concluded that the epidemiological studies to date were inadequate to establish a valid causal relationship between nitrosamine exposure and human cancer. The US EPA (1980) also concluded that it was highly improbable that humans are refractory to the carcinogenic effects of nitrosamines considering the number of animal species that show increased tumor incidence following nitrosamine exposure. IARC (1978) concluded: "Although no epidemiological data were available, N-nitrosodi-n-butyl amine should be regarded, for practical purposes, as if it were carcinogenic to humans."

Animal Studies

Groups of DB rats were exposed to NDBA in the drinking water for an unspecified duration (Druckrey *et al*., 1967). The rats were exposed to 10, 20, 37, and 75 mg/kg-day NDBA. The incidence of liver carcinomas and adenomas was 2/10, 4/10, 13/16, and 4/4, respectively. No data on control rats were reported. Median time-to-tumor decreased from 540 days at 10 mg/kg - day, to 150 days at 75 mg/kg - day.

Male Wistar rats (15 total) were exposed for 24 weeks to 0.05% NDBA in drinking water (Okajima *et al*., 1971). Nine animals served as controls. At the end of this period, the 12 remaining animals were necropsied and found to have papillomas of the bladder. Eleven of the 12 animals had bladder carcinomas, 4 had hepatocellular carcinomas, and all had papillomas or carcinomas of the esophagus. The increased incidence of bladder carcinomas and esophageal

tumors was statistically significant compared to the control group ($p < 0.001$). The incidence of liver carcinomas was not statistically different from controls ($p < 0.083$).

A group of 20 male Fischer-F344 rats was exposed to 5.4 mg NDBA by gavage twice per week for 30 weeks (Lijinsky and Reuber, 1983). Six animals survived to 100 weeks. Three animals survived to the end of the 108-week experiment. All treated animals were necropsied and examined for tumors. Of the 20 treated animals, liver carcinomas were observed in 12, lung carcinomas and adenomas in 9 and 4, respectively, forestomach cancer in 10, and bladder cancer in 7. In the control group of 20 male rats, one animal had a lung carcinoma, but no carcinomas of the esophagus, liver, or bladder were observed. The incidences of liver, lung, forestomach, and bladder carcinomas were significantly increased over controls ($p < 0.001$, 0.004, 0.001, and 0.004, respectively.).

A group of 42 male Fischer F344 rats were exposed to 0.005% (50 ppm) NDBA for 4 weeks (Imaida and Wang, 1986). The rats were followed for 100 weeks post-exposure and the median survival was 93 weeks. Esophageal cancer (unspecified type) was found in 26 of the 42 animals and esophageal papillomas in 7 of 42. In addition, liver nodules and carcinomas were found in 8/42 and 3/42 treated animals, respectively, and forestomach papillomas and carcinomas occurred in 6/42 and 2/42 treated animals, respectively. Bladder papillomas and carcinomas were found in 5/42 and 2/42 treated animals, respectively. In the control group of 39 animals, 2 animals had liver nodules, but no other tumors were detected.

Tsuda *et al*. (1987) exposed groups of 20 male F344 rats to 650, 1250, and 2500 ppm NDBA in the diet for 2 weeks. The rats were then fed an untreated diet for 50 weeks, at which time the animals were killed and necropsied. The incidence of bladder papillomas and hepatocellular carcinomas are shown in Table 1.

Table 1. Tumor incidence in male F344 rats exposed to diet containing N-nitroso-N-dibutylamine (NDBA) (Tsuda *et al*., 1987)

NDEA Treatment Group (ppm in diet)	Bladder papillomas	Hepatocellular carcinomas
650	2/20	0/20
1250	2/20	2/20
2500	4/20	4/20

Male ICR mice (39 total) were exposed to 50 ppm NDBA in the diet for 12 months (Takayama and Imaizumi, 1969). Of the surviving 33 mice at the end of 12 months, 27/33 had squamous cell carcinomas of the forestomach, 15/33 developed liver tumors (5 trabecular hepatomas and 10 adenomas), 8/33 developed lung adenomas, and 4/33 developed esophageal papillomas. Examination of the 28 surviving control animals revealed that 2 had lung adenomas, but no other tumors were reported in the controls.

Male or female C57Bl/6 mice (50/sex/group) were exposed to 60 or 240 ppm NDBA in their drinking water from age 10-12 weeks until moribund or dead (Bertram and Craig, 1970). The

incidence of bladder carcinomas in males was 17/47 and 36/45 at the 60 and 240 ppm concentrations, respectively. Females developed bladder carcinomas with an incidence of 2/42 and 8/45 for the 60 and 240 ppm groups, respectively. Esophageal papillomas were found in 45/47 and 40/42 for males and 40/42 and 45/45 for females at the 60 and 240 ppm groups, respectively. No data on unexposed controls were presented.

Male and female Syrian Golden Hamsters (5/sex/group) were given single doses of 400, 800, or 1600 mg/kg NDBA by gavage; groups of 20 males or females served as controls (Althoff *et al*., 1973). Animals were observed for their lifespan and were killed when moribund. Mean survival times were affected in a dose-dependent manner; controls survived 63.5 weeks, and low-, medium- and high-dose groups survived for 59.6, 54.5, and 49.3 weeks, respectively. Respiratory neoplasms (unspecified type) were found in 0/40, 3/10, 5/10 and 7/10 hamsters of the control, low-, medium-, and high-dose groups, respectively. In a later study, Althoff *et al*. (1974) exposed groups of 20 (10/sex/group) male and female Syrian Golden hamsters to 0, 29, 58, 116, 232, or 464 mg/kg NDBA once pre week for life. In this study, the incidences of respiratory neoplasms were 0/20, 0/20, 0/19, 2/16, 12/20, and 8/16 for the groups exposed to 0, 29, 58, 116, 232, or 464 mg/kg NDBA, respectively.

Several studies in mice, rabbits and hamsters have shown NDBA to be carcinogenic following subcutaneous injection (Fuji *et al*., 1977; Flaks *et al*., 1973; Althoff *et al*., 1973 & 1974; Reznik *et al*., 1976; Cohen *et al*., 1975).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The study by Bertram and Craig (1970) was used by CDHS (1988) to derive the cancer potency for NDBA. The upper bound estimate of cancer potency from these data is the most reliable upper bound from dose-response data in sensitive species.

The upper 95% bound on the multistage polynomial could not be determined from the tumor incidence data in two other studies: Althoff *et al*. (1974) and Okajima *et al*. (1971). The potency estimates from the studies by Lijinsky and Reuber (1983), and Takayama and Imaizumi (1971) both rely on assumptions about the time of sacrifice and corrections for less than lifetime dosing.

Methodology

The study by Bertram and Craig (1970) showed that several organ sites developed tumors in both sexes of mice exposed to NDBA. The combined incidence of bladder and esophageal neoplasms in male mice was used for the potency estimate. These data depict the most reliable dose-response for the most sensitive site and species.

A linearized multistage model was used to estimate the cancer potency of NDBA from the Bertram and Craig. (1970) data in male C57Bl/6 mice (Crump *et al*., 1982). The 95% upper

confidence bound on the dose-response slope was used to derive the human cancer potency value.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. In this case, the scaling factor was equal to 1. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 10.8 $[mg/kg \times day]^{-1}$ was calculated for NDBA (CDHS, 1988). An airborne unit risk factor of 1.0E-2 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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U.S. Environmental Protection Agency (US EPA). 1988. Integrated Risk Information System (IRIS): N-Nitrosodiethylamine. EPA Office of Research and Development, Washington, DC.

N-NITROSO-*N*-METHYLETHYLAMINE

CAS No: 10595-95-6

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	88.13
Boiling point	163ºC
Melting point	not available
Vapor pressure	not available
Conversion factor	1 ppm = 3.61 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.3 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 3.7 E+0 $(mg/kg\text{-}day)^{-1}$
[Female rat hepatocellular carcinoma data (Druckrey *et al*., 1967), one hit model, time to tumor incidence (US EPA, 1993), cross-route extrapolation]

III. CARCINOGENIC EFFECTS

Human Studies

No human carcinogenicity data on specific exposure to N-nitroso-N-methylethylamine (NMEA) have been reported. Human exposure to nitrosamines is usually the result of exposure to complex mixtures containing these compounds (e.g. cutting oils, tobacco products). Carcinogenicity data on these mixtures are of limited use in evaluating the carcinogenicity of individual nitrosamines because of the presence of other potentially confounding substances.

Animal Studies

Fifteen female BD rats were exposed to N-nitroso-N-methylethylamine (NMEA) in drinking water at doses of approximately 1 mg/kg/day (4 rats) or 2 mg/kg/day (11 rats). Exposure was continuous for the lifetime of the animals. Nine of 15 animals developed hepatocellular carcinomas and one developed a fibrosarcoma of the vagina. Average tumor induction times and total doses to produce tumors in 50% of the animals were 500 days and 0.42 g/kg for the low dose group and 360 days and 0.75 g/kg for the high-dose group. No control group was included in this study (Druckrey *et al*., 1967; reviewed in IARC, 1974 and US EPA, 1993).

DMEA also induced hepatocellular carcinomas (19/20 animals), hemangiosarcomas (17/20) and cholangiocarcinomas (3/20) with accompanying lung metastases and esophageal papillomas and carcinomas in male and female Fisher 344 (F344) rats (20/group) (Lijinsky and Reuber, 1981). Study animals received drinking water (20 ml/day/rat) containing 150 mg/l DMEA 5 days/week (tap water provided on the untreated days) for 30 weeks (total dose 450 mg) with lifetime observation. Untreated control groups were not included in this study. In a similar study, male

F344 rats dosed with 600 µg or 3000 µg DMEA/week (6 or 30 mg/l in drinking water 5 days/week) for 30 weeks developed tumors. Three of 20 animals in the low-dose group developed hepatocellular carcinomas; 12 of 20 animals in the high-dose group developed hepatocellular carcinomas, nasal tumors and esophageal papillomas (Lijinsky and Reuber, 1980). This study also did not include an untreated control group. Liver (hepatocellular carcinoma; 9/20 animals) and nasal cavity (4/20 animals) tumors were also observed in male F344 rats exposed to drinking water containing 30 mg/l NMEA 5 days/week for 30 weeks (total dose 90 mg) (Lijinsky *et al*., 1982). In contrast, the only possibly exposure-related increase in tumor incidence seen in female F344 rats receiving drinking water containing 6 mg/l NMEA was an increased leukemia incidence (18/20 treated compared to 12/20 controls) (Lijinsky *et al*., 1983).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The study by Druckrey *et al*. (1967) in which 9 of 15 female BD rats exposed to 1 mg/kg/day (4 rats) or 2 mg/kg/day (11 rats) DMEA in drinking water over their lifetime developed hepatocellular carcinomas was chosen as the basis of a cancer potency factor for NMEA. This study used lifetime exposure to NMEA in a sensitive species and sex.

Methodology

A one-hit model was fitted to time-to-tumor data from the study by Druckrey *et al*. (1967). The dose associated with a lifetime risk of 0.5 was calculated as follows:

$$d = Ck/(t_{50})^n = \frac{88.1\ \text{mg/mmol} * 0.81 \times 10^4\ \text{mmol/kg/day}}{(728)^{2.3}}$$

where C is the conversion between mmol and mg, k is an empirically derived constant (carcinogenicity index) (Druckrey *et al*., 1967), t_{50} is the median time of tumor induction in days, and n is an empirically generated representative value for dialkylnitrosamines (Druckrey *et al*., 1967). This relationship was derived from experimental data from studies on a number of different N-nitroso compounds. The one-hit model was used to derive a cancer potency factor of 3.72 $(\text{mg/kg/day})^{-1}$. Adjusting this factor by the cube root of the human body weight/assumed rat body weight ratio $[(70\ \text{kg}/0.35\ \text{kg})^{1/3}]$ results in a human cancer potency factor of 2.2 E+1 $(\text{mg/kg/day})^{-1}$. A unit risk of 6.3 E-3 $(\mu\text{g/m}^3)^{-1}$ was then calculated by OEHHA/ATES from the cancer potency factor (20 m^3/day inspiration rate).

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U.S. Environmental Protection Agency 1993. Integrated Risk Assessment System: N-Nitroso-N-methylethylamine. Office of Health and Environmental Assessment, Washington, DC.

N-NITROSODI-N-PROPYLAMINE

CAS No: 621-64-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	130.12
Boiling point	not available
Melting point	not available
Vapor pressure	0.086 mm Hg @ 20°C
Air concentration conversion	1 ppm = 5.3 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.0 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 7.0 E+0 $(mg/kg\text{-}day)^{-1}$
[calculated from a cancer slope factor derived by US EPA (1986)]

III. CARCINOGENIC EFFECTS

Human Studies

No studies addressing the carcinogenicity of N-nitrosodi-n-propylamine to humans have been conducted.

Animal Studies

Druckrey *et al.* (1967) treated a total of 48 BD rats (sex unspecified) orally with N-nitrosodi-n-propylamine at concentrations of 4, 8, 15, or 30 mg/kg body weight 7 days per week for life (16, 16, 15, and 1 animal, respectively). An untreated control group was not included in the study, although background tumor incidence was reported to be negligible. Liver carcinoma incidence was 14/16, 15/16, 15/15, and 1/1 in the four dose groups, respectively. Tumor induction time was dose-related. The authors also note tumors of the esophagus (8/48) and tongue (6/48).

Lijinsky and Taylor (1978, 1979) exposed 15 male Sprague-Dawley rats to N-nitrosodi-n-propylamine in drinking water 5 days/week for 30 weeks at 1.8 mg/day resulting in a daily dose of 5.1 mg/kg-day. No control group was included. Liver carcinomas (9/15), esophageal papillomas (6/15) and carcinomas (8/15), and nasal adenocarcinomas (8/15) were observed among exposed rats.

Lijinsky and Reuber (1981) exposed 20 Fischer 344 rats (sex unspecified) to N-nitrosodi-n-propylamine in drinking water at 0.9 mg/day for 5 days/week for 30 weeks resulting in a daily

dose of 2.6 mg/kg-day. No control group was included. Esophageal carcinomas (20/20) and forestomach tumors (12/20) developed in exposed animals.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

US EPA (1986) based its selection of a cancer potency on a study which demonstrates induction of liver tumors by N-nitrosodi-n-propylamine. US EPA (1986) used the data from Druckrey *et al.*(1967) in the induction of hepatocellular carcinoma in BD rats exposed to N-nitrosodi-n-propylamine in drinking water to calculate a cancer potency value.

Methodology

The high tumor incidence in all the N-nitrosodi-n-propylamine treated animals suggests time-dependent analysis is more appropriate than multistage analysis in the derivation of a cancer potency value. A dosage estimate for use in deriving the cancer potency value was based on the following relationship, where d is the daily dose, C is the mmol to mg conversion factor (130.2 mg/mmol), k is an empirically derived constant estimated from a plot of k versus the number of carbon atoms for lower di-N-alkylnitrosamines ($k=1.7 \times 10^4$ mmol/kg-day), t_{50} is the median time of tumor induction, and n is a representative value for dialkylnitrosamines (n=2.3; Druckrey *et al.*, 1967):

$$d = \frac{C \times k}{t_{50}^{\,n}}$$

The resulting daily dose estimate was 0.578 mg/kg-day. Applying this estimate to a rearrangement of the one-hit model gave an animal cancer potency value (q_{animal}) of 1.2 $(mg/kg\text{-}day)^{-1}$.

$$q_{animal} = -\ln(0.5/day) / d$$

Conversion of the q_{animal} to a human cancer potency estimate (q_{human}) was made based on the following relationship, where bw_h is the assumed human body weight (70 kg) and bw_a is the assumed experimental animal body weight (0.35 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting estimate of q_{human} was 7.0 $(mg/kg\text{-}day)^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.0 E-3 $(\mu g/m^3)^{-1}$.

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N-NITROSODIETHYLAMINE

CAS No: 55-18-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	102.1
Boiling point	175-177° C
Melting point	Not found
Vapor pressure	0.86 mm Hg @ 20° C
Air concentration conversion	1 ppm = 4.2 mg/m^3 @ 25° C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.0 E-2 $(\mu g/m^3)^{-1}$
Slope Factor: 3.6 E+1 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There is no direct evidence that links nitrosamines, including N-nitrosodiethylamine (NDEA), to human cancer. The US EPA (1980) concluded that the epidemiological studies to date were inadequate to establish a valid causal relationship between nitrosamine exposure and human cancer. The US EPA (1980) also concluded that it was highly improbable that humans are refractory to the carcinogenic effects of nitrosamines considering the number of animal species that show increased tumor incidence following nitrosamine exposure.

Animal Studies

A number of qualitative studies were conducted in a range of species, including rats, mice, hamsters, guinea pigs, rabbits, dogs, and monkeys (Yamamoto *et al*., 1972; Druckrey *et al*., 1967; Magee *et al*., 1976; Rajewski *et al*., 1966; Tomatis, 1973). In addition to these studies, a number of later studies show evidence of quantitative dose-response relationships.

Drinking water containing a range of concentrations from 0.033 to 16.896 ppm NDEA was administered to male and female Colworth rats (60/sex/group) for their natural lifespan (Peto *et al*., 1982; 1984). The control groups consisted of 240 rats/sex. Nearly all animals exposed to the high dose of NDEA died from tumors of the liver or esophagus (Table 1). Other sites showing an increase in tumors included the lower jaw, stomach, kidney, ovaries, seminal vesicles, and nasopharynx.

Table 1. Liver tumors in Colworth male and female rats exposed to drinking water containing N-nitrosodiethylamine (NDEA) (Peto *et al*., 1982)

NDEA concentration (ppm)	Observed deaths from liver tumors	
	males	females
0	1/240	1/240
0.033	1/60	0/60
0.066	0/60	0/60
0.132	5/60	1/60
0.264	2/60	1/60
0.528	4/60	3/60
1.056	8/60	23/60
1.584	14/60	37/60
2.112	7/60	38/60
2.640	17/60	47/60
3.168	17/60	42/60
4.224	26/60	42/60
5.280	26/60	43/60
6.336	30/60	47/60
8.448	25/60	55/60
16.896	44/60	49/60

A later analysis by Peto *et al*. (1984) showed that, in rats, the initial age of contact with NDEA was important in determining the probability of liver cancer. Young rats were much more susceptible than adults to NDEA-induced liver neoplasia than adults exposed for an equal amount of time.

Lijinsky *et al*. (1981) administered NDEA in the drinking water to 11 groups of female Fisher-344 rats (20 per group) for varying durations, up to 104 weeks. The animals were observed for their lifespan. The treatment groups are shown in Table 2.

Table 2. Treatment groups, concentrations, and durations of N-nitrosodiethylamine (NDEA) exposures in female Fisher 344 rats (Lijinsky *et al*., 1981).

Treatment Group	NDEA concentration(mg/l)	Treatment duration (weeks)
Control	0	104
1	113	17
2	45	22
3	18	30
4	7	30
5	2.8	30
6	1.1	30
7	1.1	60
8	0.45	30
9	0.45	60
10	0.45	104

Treatment related increases in the incidence of tumors were observed in the liver, forestomach, esophagus and tongue. The incidence of tumors in the animals exposed to the lowest concentration are shown in Table 3.

Table 3. Tumor incidence in female rats exposed to 0.45 mg/l N-nitrosodiethylamine (NDEA) in drinking water for 0, 30, 60, or 104 weeks (Lijinsky *et al*., 1981).

Treatment duration (weeks)	Total dose (mg) of NDEA	Esophageal carcinoma or papilloma	Forestomach papilloma	Tongue carcinoma	Liver carcinoma	Liver carcinoma or hyperplastic nodule
0	0	0/20	0/20	0/20	0/20	1/20
30	1.35	1/20	1/20	1/20	1/20	6/20
60	2.70	3/20	2/20	2/20	6/20	11/20
104	4.68	13/20	5/20	2/20	4/20	7/20

Habs and Schmahl (1980) exposed male Sprague-Dawley rats (90 per group) to 0 or 0.1 mg/kg/day NDEA in the drinking water 5 times weekly until natural death of the animals. Another group of rats received NDEA followed by a 25% solution of ethanol. Liver tumors (histological type unspecified) were observed in 0/82 controls and 36/82 NDEA-treated rats, respectively. The rats receiving ethanol in addition to NDEA showed a liver tumor incidence of 4/59. A similar pattern was seen for the development of esophageal tumors. Rats exposed to NDEA alone developed esophageal tumors (type unspecified) at a rate of 33/82. Rats exposed to NDEA and ethanol developed esophageal tumors in 18/59 cases, and controls had a tumor incidence of 0/82.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The studies by Peto *et al*. (1982; 1984) were used by CDHS (1988) to derive the cancer potency for NDEA. These studies utilized relatively large numbers of animals (60-240 per group) over a wide dose range. The Peto *et al*. (1982) study contained more information about the dose-response at the low range of experimental doses than the other studies described. Therefore, the cancer potency for NDEA was calculated from the Peto *et al*. (1982) study even though the calculated value is lower than other potency estimates from Lijinsky *et al*. (1981) or Habs and Schmahl (1980).

Methodology

The study by Peto *et al*. (1982) showed that several organ sites developed tumors in both sexes of rats exposed to NDEA. The incidence of hepatocellular neoplasms (histological designation unknown) in males resulted in the highest potency value when only the 6 lowest doses were considered. Water consumption by male rats was reported by Peto *et al*. (1984) to be 41 mL/kg/day. Low-dose group mortality did not differ significantly from that observed in the control group, therefore no time corrections were applied to the calculation.

A linearized multistage model was used to estimate the cancer potency of NDEA from the Peto *et al*. (1982) data in male Colworth rats (Crump *et al*., 1982). The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. In this case, the scaling factor was equal to 1. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the body weight of human or animal, in this case, 450 grams for male rats.

Using these relationships, a human cancer potency (q_{human}) of 36 $[mg/kg \times day]^{-1}$ was calculated for NDEA (CDHS, 1988). An airborne unit risk factor of 1.0E-2 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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N-NITROSODIMETHYLAMINE

CAS No: 62-75-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	74.1
Boiling point	151°C
Melting point	unknown
Vapor pressure	2.7 mm Hg @ 20°C
Air concentration conversion	1 ppm = 3.08 mg/m^3 @ 20°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.6 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 1.6 E+1 $(mg/kg\text{-}day)^{-1}$
[calculated from a cancer potency value derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Epidemiological studies correlating exposure to N-nitrosodimethylamine (NDMA) and human cancers are inadequate to establish a causal relationship.

Animal Studies

Terracini *et al* .(1967) exposed male and female MRC Porton rats to feed containing 0, 2, 5, 10, 20 or 50 ppm for up to 120 weeks. Daily dose rates were calculated based upon observed food consumption rates of 15 g/day. Most survivors were sacrificed at 104 weeks, with the exception of an unspecified number of animals which were sacrificed at 120 weeks. Liver tumor incidence data were grouped into those which occured among animals surviving greater than or less than 60 weeks. No liver tumors were reported among 29 untreated animals, four of which died before 60 weeks. Combined incidence data of liver tumors among female rats dying at any time during the course of the experiment were 0/18, 4/62, 2/5, 15/23, and 10/12 for the 2, 5, 10, 20, and 50 ppm dose groups, respectively. Significant dose-related increase in incidence of liver tumors and mortality in female rats was reported (level of significance not stated).

Terracini *et al.* (1973) exposed 4-5 week old female BALB/c mice to 3 ppm NDMA in drinking water for up to 80 weeks in a two generation study. The first generation treated group consisted of 62 animals and the second generation treated group consisted of 66 animals. Among first and second generation animals, an increased incidence of lung tumors was found (first generation:

44/62 treated vs. 20/62 control, $p = 10^{-5}$; second generation: 44/66 treated vs. 15/69 control, $p = 10^{-8}$).

Terao *et al.* (1978) exposed 4 week old male Wistar rats to feed containing NDMA and/or sterigmatocystin (STG) for 54 weeks. Five exposure groups included 10 ppm STG alone, 10 ppm STG and 1 ppm NDMA, 1 ppm STG and 10 ppm NDMA, 10 ppm NDMA, and a group receiving basal diet alone. Animals were sacrificed at 69 weeks with the exception of one animal from each group sacrificed after 5 weeks of exposure. Rats in all groups exposed to NDMA showed an increased incidence of Leydig-cell tumors ($p=0.002$). Liver tumors were not observed in the group receiving NDMA alone; however, liver tumor incidence was elevated in the group receiving STG alone and in the group receiving 10 ppm STG and 1 ppm NDMA.

Arai *et al.* (1979) exposed 6 week old male and female Wistar rats (7 to 17/sex/group) to feed containing 0, 0.1, 1 or 10 ppm NDMA for 96 weeks. Food intake was monitored. Treated female animals were found to have a higher incidence of nodular hyperplastic liver lesions ($p<0.05$, Fisher's exact test).

Griciute *et al.* (1981) treated 8 week old male and female C57BL mice with NDMA (0.03 mg) and/or ethanol (0.8 ml) in 0.2 ml water by intragastric intubation for 50 weeks. Control animals received only water. Survivors were sacrificed at 80 weeks. No liver tumors developed in animals receiving ethanol alone. Among animals receiving NDMA alone, the incidence of malignant liver tumors was increased over controls (14/37 treated males, $p = 10^{-5}$; 16/29 treated females, $p < 10^{-6}$). Among animals receiving both NDMA and ethanol, the incidence of forebrain olfactory neuroepithelioma was increased (24/66 treated vs. 0/66 control; $p<0.001$). No tumors of this type were observed in animals receiving NDMA or ethanol alone.

Peto *et al.* (1982, 1984) exposed Colworth rats (60/sex/group) to NDMA in drinking water at 15 concentrations ranging from 0.033 to 16.896 ppm for life. A group of 240 animals receiving only drinking water served as controls. Additional treatment groups of 6 animals/group were sacrificed at 6 and 12 months. Water consumption for male and female rats was 41 ml/kg and 72 ml/kg, respectively. Among exposed animals, the incidence of fatal liver neoplasms (see Table 1) was significantly increased over controls ($p\leq0.005$) and the increase was found to be dose-related. Other tumors with trends toward increased incidence include tumors of the lung ($p=0.004$), skin ($p=0.001$), lymphatic/hematopoietic tissues ($p=0.032$), and seminal vesicles ($p=0.004$).

Lijinski and Reuber (1984) exposed 7-8 week old female Fischer 344 rats (20/group) to NDMA in drinking water at concentrations of 13 and 5.5 mg/l for 5 days/week for 30 weeks. Animals were observed for life. Hepatocellular carcinomas, hemangiosarcomas, and neoplastic nodules were observed in treated animals. Significantly increased incidence of liver tumors of all types was observed in both low-dose (14/20 treated vs. 2/20 controls; $p = 10^{-4}$) and high-dose (19/20 treated vs. 2/20 controls; $p < 10^{-5}$) animals.

Table 1. Liver tumor incidence data in Colworth rats exposed to NDMA in drinking water (Peto *et al.*, 1982).

dose level (ppm)*	fatal liver tumor incidence	
	male	female
0	1/240	1/240
0.033	1/60	1/60
0.066	3/60	0/60
0.132	3/60	2/60
0.264	3/60	3/60
0.528	3/60	5/60
1.056	5/60	5/60
1.584	3/60	27/60
2.112	13/60	33/60
2.640	27/60	44/60
3.168	33/60	48/60
4.224	36/60	53/60
5.280	46/60	52/60
6.336	49/60	51/60
8.448	55/60	55/60
16.896	59/60	58/60

*Colworth rats (48/sex/group) were exposed to NDMA in drinking water for life.

Druckrey *et al.*(1967) exposed BD rats (sex unspecified) to NDMA by inhalation twice per week for 30 minutes. One group of 6 rats received 100 ppm NDMA and a group of 12 rats received 50 ppm NDMA. No information on a control group was reported. Tumors of the nasal turbinates were reported at the time of death in 4/6 and 8/12 of the high- and low-dose groups, respectively. Three animals in the low-dose group died prematurely (time unspecified). No liver tumors were reported in either group.

Moiseev and Benemansky (1975; reviewed in IARC, 1978) exposed Balb/c mice and Wistar rats to NDMA by inhalation at concentrations of 0.005 and 0.2 mg/m^3. Exposure duration was 17 months for mice and 25 months for rats. At 0.2 mg/m^3 NDMA, tumors of the lung, liver, and kidney were reported to arise earlier and in greater numbers than in control animals (IARC, 1978). Exposures to the lower concentration did not result in significantly increased incidence in tumors over controls.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Five studies showing tumor induction in animals by NDMA have been deemed appropriate by CDHS (1988) for the development of cancer potency values. The values derived from the studies

are presented in Table 2. The methodologies used to derive the values are described below as well as the rationale for selection of the OEHHA unit risk value for NDMA.

Methodologies

Peto *et al* .(1982, 1984) derived potency values from the incidence data of fatal liver tumors in male and female Colworth rats. The cumulative risk was calculated based on the assumption that the risk increases with the seventh power of exposure duration and the observation that a dose of 1.0 μg/kg-day results in a 0.03-0.04% incidence of liver tumors at two years. Estimated cancer potency at low doses (q_{animal}) was found to be 0.29 and 0.4 $(mg/kg\text{-}day)^{-1}$ for male and female rats, respectively. Peto *et al.* (1982,1984) also scaled these potencies up by a factor of 7 to account for calculated increased risk from the observation that median experimental animal lifespan was beyond 2 years in this study. Conversion to human potency values (q_{human}) was based on the body weight scaling relationship described below, with an assumed human body weight (bw_h) of 70 kg and experimental animal body weights (bw_a) of 450 and 250 g for male and female rats:

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting q_{human} values were 12 and 16 $(mg/kg\text{-}day)^{-1}$ from the male and female rat data, respectively.

Dose rate estimates of 0.82 mg/kg-day for female BALB/c mice receiving NDMA in drinking water in the study by Terracini *et al.* (1973) were based on a US EPA (1988) reference animal body weight value and water consumption rate (CDHS, 1988). Using a multistage model, experimental potencies (q_1^*) derived from this dose rate using the incidence of lung tumors in F_0 and F_1 generation animals were 1.5 and 1.6 $(mg/kg\text{-}day)^{-1}$, respectively. Potency in animals (q_{animal}) was estimated assuming cancer incidence increases with the third power of age, with T_e the experimental duration and T the natural lifespan of the animals (104 weeks):

$$q_{animal} = q_1^* \times (T/T_e)^3$$

Further conversion to human cancer potencies with a body weight scaling factor were made as described for Peto *et al.*(1982,1984) resulting in human potency estimates (q_{human}) of 49 and 53 $(mg/kg\text{-}day)^{-1}$ from the F_0 and F_1 generation mouse tumor incidence data, respectively.

High- and low-dose rates estimates of 0.80 and 0.35 mg/kg-day in the study by Lijinsky and Reuber (1984) were based on US EPA (1988) animal body weight reference values in the induction of liver tumors in Fischer 344 rats (CDHS, 1988). Using the Crouch (1983) correction for variable dosing and a multistage model, the animal cancer potency estimate (q_{animal}) was 5.8 $(mg/kg\text{-}day)^{-1}$. Using the body weight conversion factor as described in the Peto *et al.* (1982, 1984) potency derivation (bw_a=0.229 kg; US EPA, 1988), the resulting q_{human} was 39 $(mg/kg\text{-}day)^{-1}$.

Dose rate estimates to MRC Porton rats exposed to NDMA in diet in the study by Terracini *et al.* (1967) were made by the method of Crouch (1983) to account for variable dosing during the

course of the experiment (CDHS, 1988). Using liver tumor incidence among female rats surviving less than 60 weeks, a q_{animal} value of 5.8 $(mg/kg\text{-}day)^{-1}$ was derived from a multistage model. Conversion to q_{human} based on a body weight scaling factor resulted in a potency value of 34 $(mg/kg\text{-}day)^{-1}$. Using liver tumor incidence of animals surviving more than 60 weeks resulted in a q_{human} value of 7.6 $(mg/kg\text{-}day)^{-1}$; however, this value may be an underestimate because of early mortality in exposed animals.

Arai *et al.* (1979) estimated an NDMA dose rate of 0.018 and 0.033 mg/kg-day for male and female Wistar rats, respectively, based on experimentally reported food consumption rates and animal body weights. Applying a multistage model to the incidence of liver fibrosarcoma in male rats resulted in an estimated q_{animal} of 5.0 $(mg/kg\text{-}day)^{-1}$. Similarly, a q_{animal} for incidence of liver cancer in female rats was found to be 3.8 $(mg/kg\text{-}day)^{-1}$. The resulting q_{human} values from each of these tumor types were 29 and 25 $(mg/kg\text{-}day)^{-1}$, respectively.

Terao *et al.* (1978) demonstrated induction of Leydig-cell tumors in male Wistar rats fed diet containing NDMA. Dose rate calculations of 0.736 mg/kg-day were based on US EPA (1988) reference food intake and body weight values (CDHS, 1988). The dose correction method of Crouch (1983) was applied to account for variable dosing during the course of the experiment. Applying a multistage model to the tumor incidence data resulted in a q_{animal} value of 5.8 $(mg/kg\text{-}day)^{-1}$. The corresponding q_{human} value based on the body weight conversion factor was 31 $(mg/kg\text{-}day)^{-1}$.

Table 2. Cancer potencies derived from animal studies.

Study	Tumor type	Sex	q_{human} $(mg/kg\text{-}day)^{-1}$
Peto *et al.*(1982,1984)	fatal liver tumor	male female	12 16
Terracini *et al.*(1973)	lung tumor	F_0 female F_1 female	49 53
Lijinsky and Reuber (1984)	liver tumor	female	39
Terracini *et al.*(1973)	liver tumor	female	34
Arai *et al.* (1979)	liver fibrosarcoma liver cancer	male female	29 25
Terao *et al.*(1978)	Leydig cell tumor	male	31

Cancer potency estimates from these studies range from 12 to 53 $(mg/kg\text{-}day)^{-1}$. Of these, the q_{human} values from the Peto *et al.* (1982,1984) study were derived from the experiment with the lowest daily dose rate and the data, therefore, are most appropriate for performing a low-dose risk extrapolation. Although the q_{human} values from Peto *et al.* (1982,1984) are lower than those derived from other studies, the fact that this study was conducted at low-doses and demonstrated sensitive and significant induction of liver tumors indicates it is useful for estimation of the cancer potency of NDMA. Furthermore, the other studies were neither as large in scale nor as long in duration, suggesting potency estimates from these studies may be overly conservative and

not as representative of the true value. The most sensitive q_{human} value of 16 $(mg/kg\text{-}day)^{-1}$ derived from Peto *et al.* (1982,1984) was therefore adopted as a cancer potency value.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 4.6 E-3 $(\mu g/m^3)^{-1}$.

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N-NITROSODIPHENYLAMINE

CAS No: 86-30-6

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	198.2
Boiling point	66.5°C
Melting point	unknown
Vapor pressure	0.1 mm Hg @ 25°C
Air concentration conversion	1 ppm = 8.1 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.6 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 9.0 E-3 $(mg/kg\text{-}day)^{-1}$
[calculated from a cancer potency value derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There are no human carcinogenicity studies available for N-nitrosodiphenylamine (NDPA).

Animal Studies

Seven day-old $B6C3F_1$ and $B6AKF_1$ mice (18/sex/group) were treated with 1000 mg NDPA in dimethyl sulfoxide per kg body weight by oral gavage for 4 weeks (initial dose was not adjusted) (NTIS, 1968; Innes *et al.*, 1969). Mice were then exposed to 3769 ppm NDPA in feed to 79 weeks of age. Animals were observed for a total of 18 months. Among male $B6C3F_1$ mice, 6/15 surviving animals developed hepatomas versus 1/17 matched controls. Among female $B6AKF_1$ mice, 3/18 developed lung adenomas versus 0/17 matched controls. No statistically significant increases in tumor incidence were reported by NTIS (1968). However, a re-analysis of incidence data by current methodology showed significant increases in hepatoma incidence among male $B6C3F_1$ mice ($p=0.027$ by Fisher's exact test) and borderline significant increase in lung adenoma incidence among female $B6AKF_1$ mice ($p=0.07$) (CDHS, 1988).

$B6C3F_1$ mice (50/sex/group) were fed diet containing NDPA at two dose levels (NCI, 1979; Cardy *et al.*, 1979). Male mice received either 10000 or 20000 ppm NDPA in their diet for 101 weeks. The low- and high-dose groups of female mice received 5000 or 10000 ppm NDPA , respectively, for 38 weeks, no NDPA for 3 weeks, then 1000 or 4000 ppm NDPA for 60 weeks. Groups of 20 mice/sex fed only standard diet served as controls. No statistically significant

increases in tumor incidence were observed over controls. Some incidence of epithelial hyperplasia of the urinary bladder was noted which was not seen in control animals.

Six-week old Fischer 344 rats (50/sex/group) were exposed to diet containing 1000 or 4000 ppm NDPA for 100 weeks, with groups of 20 rats/sex serving as controls (NCI, 1979; Cardy *et al.*, 1979). No dose-related increase in mortality was observed in male mice; however, a dose-related increase in mortality was observed in females ($p=0.024$). Among male rats, incidence of transitional-cell carcinoma of the urinary bladder was 16/45 in the high-dose group, 0/46 in the low-dose group, and 0/19 in the control animals ($p=0.001$). Among female rats, incidence of transitional-cell carcinoma of the bladder was 40/49 in the high-dose group, 0/46 in the low-dose group, and 0/18 in the control animals ($p<0.001$). Among male mice, a dose-related trend in increased incidence of fibroma of the subcutis and skin was observed ($p=0.003$).

Argus and Hoch-Ligeti (1961) treated 25 male Wistar rats (92 g average body weight) with 1070 μg NDPA in 1 ml of 1.1% aqueous methylcellulose by oral gavage for 45 weeks, 5 days per week. At 53 weeks, all rats were alive and upon autopsy, no tumors were observed.

Druckrey *et al.* (1967) exposed 20 BD rats (sex unspecified) to NDPA in drinking water at a daily dose of 120 mg/kg body weight. No tumors were observed within 700 days.

Iverson (1980) applied 0.1 ml of 1% NDPA in acetone weekly for 20 weeks to the interscapular skin of 16 male and 24 female hairless hr/hr Oslo mice. Appropriate control mice were not included. Upon necropsy at 80 weeks, lung adenomas were observed in three of the 14 male survivors.

Boyland *et al.* (1968) injected 6-7 week old male CB rats (24/group) intraperitoneally with 2.5 mg NDPA in polyethylene glycol 400 once per week for six months. Control animals were injected with vehicle alone. After 2 yrs of observation, one of five treated and one of ten control rats which survived the treatment had hepatomas. One treated rat also had a pituitary adenoma.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Two animal studies described above are adequate for the derivation of cancer potency values for N-nitrosodiphenylamine. The studies initiated by Cardy *et al.* (1979) and Innes *et al.* (1969) were conducted with adequate numbers of animals and with appropriate controls such that statistically significant increases in tumor incidence were established. Cardy *et al.* (1979) report increased incidence of transitional-cell carcinomas of the bladder in male and female Fischer 344 rats. Innes *et al.*(1969) report increased incidence of hepatomas in male $B6C3F_1$ mice. The derivation of cancer potency values from these studies and the selection of a reference unit risk value are described below.

Methodology

Dosage estimates of NDPA from the Cardy *et al.* (1979) study were made based on reference body weights of 0.380 and 0.229 kg and daily food consumption rates of 0.030 and 0.021 kg for male and female mice, respectively. The resulting daily dosage calculations are 79 and 92 mg/kg-day for males and females, respectively, for the groups fed 1000 ppm in their diet, and 316 and 368 mg/kg-day for males and females, respectively, for the groups fed 4000 ppm in their diet. Fitting a multistage model to the incidence data for transitional-cell carcinoma of the bladder gives upper 95% confidence bounds on the cancer potency (q_1^*) of 0.00050 and 0.00048 $(mg/kg\text{-}day)^{-1}$ for male and female rats, respectively (Crump and Howe (1984)).

Calculation of the cancer potency for animals (q_{animal}) can be made using q_1^* and the following relationship, where T is the natural lifespan of the animal (104 weeks) and T_e is the experimental duration (100 weeks):

$$q_{animal} = q_1^* \times (T/T_e)^3$$

The resulting q_{animal} values of 0.00056 and 0.00050 $(mg/kg\text{-}day)^{-1}$ for male and female rats, respectively, can be converted to human cancer potency values (q_{human}) based on the following relationship, where bw_{animal} is the assumed body weight for the test species and bw_{human} is the assumed human body weight (reference values from US EPA (1986)):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting estimates of q_{human} are 0.0032 and 0.0034 $(mg/kg\text{-}day)^{-1}$.

Daily dosage estimates for animals from the Innes *et al.*(1969) study were made with estimates of food consumption rates of 12% and 13% for male and female mice, respectively, based on Gold *et al.* (1984). During the oral gavage dosing period (days 7 to 28) it is assumed that a linear threefold increase in body weight occurs. The method of Crouch (1983) was used to account for variable dosing during the study period. Calculations of daily dosage are 444 and 476 mg/kg-day for male and female mice, respectively. Fitting the linear model below to the significant tumor incidence data for hepatomas in male $B6C3F_1$ mice results in a cancer potency estimate (q_{animal}) of 0.0046 $(mg/kg\text{-}day)^{-1}$. In this relationship, D is the estimated daily dose, $p(T_e)$ is the probability of dying with a tumor at time T_e, and A is the background (control) tumor incidence.

$$q_{animal} = \frac{-\ln[1 - p(T_e)] - A}{D}$$

Conversion of the q_{animal} to q_{human} is achieved as described for the Cardy *et al.* (1979) data, with an assumed experimental animal body weight (bw_{animal}) of 0.03 kg. The resulting q_{human} for this study is 0.061 $(mg/kg\text{-}day)^{-1}$.

Selection of a reference cancer potency value comes from identification of the most sensitive site, species, sex and study, in the absence of evidence that the data are not representative. The Innes *et al.*(1969) study presents the highest, and thus most sensitive, cancer potency value of

0.061 $(mg/kg\text{-}day)^{-1}$. The lower 95% confidence bound on the Innes *et al.* (1969) potency value also exceeds the potency values derived from Cardy *et al.* (1979) indicating the mouse strain used by Innes *et al.* (1969) may be more sensitive. The small number of animals used in this preliminary study, however, suggests the possibility this value may be overly conservative. The two q_{human} values for NDPA in male and female rats derived from Cardy *et al.* (1979) are close, 0.0032 and 0.0034 $(mg/kg\text{-}day)^{-1}$, respectively. Since these data were derived from a large, thorough study, the development of a reference cancer potency value should include these values. The potency estimate was therefore derived from the geometric mean of the three q_{human} values described above according to the approach of Anderson *et al.* (1983). The resulting reference q_{human} is 0.009 $(mg/kg\text{-}day)^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.6 E-6 $(\mu g/m^3)^{-1}$.

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p-NITROSODIPHENYLAMINE

CAS No: 156-10-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	198.24
Boiling point	not available
Melting point	144-145 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 8.1 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.3 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 2.2 E-2 $(mg/kg\text{-}day)^{-1}$
[Male rat liver tumor data (NCI, 1979), contained in Gold *et al.* (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *p*-nitrosodiphenylamine in humans are known to exist.

Animal Studies

Male and female Fischer 344 rats and $B6C3F_1$ mice were fed diets containing technical grade *p*-nitrosodiphenylamine (73% active material, 25% water, unspecified impurities). Rats were fed diets containing 2500 or 5000 mg/kg diet *p*-nitrosodiphenylamine for 78 weeks, followed by a 27 week observation period. Mice were fed diets containing either 5000 mg/kg diet *p*-nitrosodiphenylamine for 40 weeks, then 2500 mg/kg diet for 17 weeks, or 10000 mg/kg diet for 40 weeks, followed by control diet for 7 weeks, then 5000 mg/kg for 10 weeks. Both dose groups were then maintained on control diet for an additional 35 weeks. Treatment groups consisted of 50 animals/sex/species/group; matched control groups consisted of 20 animals/sex/species and were kept under observation for 105 and 92 weeks for rats and mice, respectively. Rat survival was 90, 86 and 92% for males and 85, 84 and 92% for females in the control, low-dose and high-dose groups, respectively. Mouse survival was 85, 88 and 60% for males and 90, 84 and 52% for females in the control, low-dose and high-dose groups, respectively. Significant increases in the incidence of liver tumors (neoplastic nodules, hepatocellular adenomas and carcinomas) was noted in treated male mice and rats. Tumor incidence data is listed in Table 1.

Table 1. *P*-Nitrosodiphenylamine-induced liver tumor incidence in male Fischer 344 rats and B6C3F$_1$ mice (NCI, 1979)

Species	Dose group	Average dose[1] (mg/kg-day)	Tumor incidence[2]
rat	control	0	0/20
	low dose	74.3	10/50
	high dose	149	19/50
mouse	control	0	2/20
	low dose	316	22/50
	high dose	587	12/50

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al.* (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The results of NCI (1979) feeding studies of *p*-nitrosodiphenylamine in male and female F344 rats and B6C3F$_1$ mice are listed by Gold *et al.* (1984). NTP (1991) characterizes the studies in male rats and male mice as positive. Significant increases in malignant liver tumors were observed in males of both species, with rats displaying greater sensitivity to the compound. However, survival was significantly reduced in the study in male mice, so the apparently lower sensitivity of these animals may have been due to the fact that they were at risk for a shorter time period than the rats. Cancer potency is based on the dose-response data for liver tumors in male rats as seen in Table 1 (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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N-NITROSOMORPHOLINE

CAS No: 59-89-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	116.11
Boiling point	224-225 °C (@ 747 mm Hg)
Melting point	29 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.75 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.9 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 6.7 E+0 $(mg/kg\text{-}day)^{-1}$
[Female hamster respiratory tract tumor data (Ketkar *et al*., 1983), contained in Gold *et al.* (1987) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of N-nitrosomorpholine in humans are known to exist.

Animal Studies

IARC (1978) reviewed a study in which 58 male NMRI mice were exposed to N-nitrosomorpholine in drinking water at a concentration of 100 mg/l for the life of the animals (Bannasch and Müller, 1964; Müller, 1964). Increases in liver tumor incidence were noted; 16/58 animals developed hepatocellular adenomas. Treated animals also developed "numerous" lung adenomas and one lung squamous cell carcinoma was observed. Only 1/17 controls developed lung adenomas.

Male and female MRC rats (15 animals/sex) were exposed to *N*-nitrosomorpholine in drinking water (100 mg/l; total dose 500 mg) for 50 weeks, then observed for the life of the animal (Garcia and Lijinsky, 1972). Male and females displayed increased incidences of liver tumors (hepatocellular carcinomas and hemangioendotheliomias; 13/15 and 13/14 in males and females, respectively) and nasal cavity tumors (9/15 and 5/14 in males and females, respectively). The study did not report that a control group was included.

Male and female Syrian golden hamsters (20/sex/group) were given weekly subcutaneous injections of *N*-nitrosomorpholine, which were one-fifth, one-tenth or one-twentieth of the LD50

of *N*-nitrosomorpholine, for life (Haas *et al*., 1973). Males received 24.6, 49.2 or 98.4 mg/kg body weight; females recieved 28.1, 56.2 or 112.4 mg/kg body weight. Treatment-related increases in the incidence of respiratory tract tumors (primarily in the nasal cavity and trachea) were observed.

Lijinsky *et al*. (1976) exposed male Sprague-Dawley rats (30/exposure group) to *N*-nitrosomorpholine in drinking water (8 or 40 mg/l, 5 days/week; total dose 0.21 and 1.05 mM, respectively) for 30 weeks. The animals were then observed for the remainder of their lifetime. Hepatocellular (benign or malignant) tumors were reported in 11/30 and 16/30 low- and high-dose animals, respectively. Hemangioendothelial tumors were reported in 1/30 and 2/30 low- and high-dose animals, respectively. The authors did not report the inclusion of a control group in this study.

Ketkar *et al*. (1983) exposed male and female Syrian golden hamsters (30/sex/group) to 0.001, 0.005 or 0.01% *N*-nitrosomorpholine in the drinking water for life; untreated control groups (50 animals/sex) were also included. Increased incidences of benign and malignant tumors of the respiratory tract (primarily papillary polyps, papillomas and epidermoid carcinomas of the larynx and trachea) and the gastrointestinal tract (primarily liver tumors, including hepatocellular adenomas and carcinomas) were observed in both males and females. No corresponding tumors were observed in the control groups. Tumor incidence data is listed in Table 1.

Table 1. *N*-nitrosomorpholine-induced tumor incidence in male and female Syrian golden hamsters (Ketkar *et al*., 1983)

Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
male controls	0	respiratory tract	0/50
male low dose	1.2		8/29
male mid dose	6		13/29
male high dose	12		21/30
male controls	0	liver tumors	0/50
male low dose	1.2		4/29
male mid dose	6		9/29
male high dose	12		18/30
female controls	0	respiratory tract	0/50
female low dose	1.36		14/28
female mid dose	6.82		16/30
female high dose	13.6		22/30
female controls	0	liver tumors	0/50
female low dose	1.36		0/28
female mid dose	6.82		2/30
female high dose	13.6		6/30

1. Doses as reported by Gold *et al.* (1987).
2. Tumor incidences as reported by Gold *et al.* (1987).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al*. (1987) list results from a drinking water study in male and female Syrian Golden hamsters (Ketkar *et al.*, 1983). Tumors of the respiratory system and liver were observed at significant levels in both sexes; females were slightly more sensitive than males. Cancer potency for N-nitrosomorpholine is based on tumors of the respiratory system, the more sensitive site, in female hamsters (see Table 1) (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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N-NITROSOPIPERIDINE

CAS No: 100-75-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	114.15
Boiling point	217 °C (@ 721 mmHg)
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.7 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.7 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 9.4 E+0 $(mg/kg\text{-}day)^{-1}$
[Rat liver tumors (Eisenbrand *et al*., 1980), contained in Gold *et* al. (1987) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *N*-nitrosopiperidine in humans are known to exist.

Animal Studies

Takayama (1969) fed 33 male ICR mice diets containing 50 mg/kg *N*-nitrosopiperidine for a period of 12 months; a 30 animal untreated control group was included. An increased incidence of forestomach (squamous cell carcinoma), liver and lung (adenomas) tumors were observed in treated animals when compared to controls. Tumor incidence data is listed in Table 1.

Table 1. *N*-nitrosopiperidine-induced tumor incidence in male ICR mice (Takayama, 1969)

Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
controls	0	forestomach liver lung	0/30 0/30 2/30
treated	6	forestomach liver lung	18/33 6/33 10/33

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al.* (1984).

Male and female Sprague-Dawley rats were exposed to *N*-nitrosopiperidine in the drinking water 5 days/week for the life of the animals at exposure levels of 0, 0.024, 0.12, 0.6 and 3 mg/kg body weight (group sizes were 40, 78, 75, 34 and 34 animals, respectively) (Eisenbrand *et al*., 1980). Significant increases were noted in the incidence of esophageal squamous cell carcinomas and liver tumors (hemangioendotheliomas, and hepatocellular adenomas and carcinomas). Tumor incidence data is listed in Table 2.

Table 2. Induction of liver tumors in male and female Sprague-Dawley rats by *N*-nitrosopiperidine (Eisenbrand *et al*., 1980)

Dose group $(mg/kg/day)^{-1}$	Average dose[1] $(mg/kg/day)^{-1}$	Tumor incidence[2]
0	0	0/40
0.024	0.0171	3/78
0.12	0.0857	5/75
0.6	0.429	16/34
3.0	2.14	11/34

1. Doses as reported by Gold *et al.* (1987).
2. Tumor incidences (males and females combined) as reported by Gold *et al*. (1987).

Adamson and Sieber (1982) exposed male and female rhesus and cynomolgus monkeys to *N*-nitrosopiperidine by gavage (400 mg/kg body weight, 5 days/week; average dose 279 and 280 mg/kg-day for cynomolgus and rhesus monkeys, respectively); male and female rhesus monkeys were also exposed to *N*-nitrosopiperidine by intraperitoneal injection (40 mg/kg body weight; average dose 5.59 mg/kg). Exposure and total experimental (exposure and untreated observation period) durations were 90 and 92 months, respectively for cynomolgus monkeys, 8 and 9 years, respectively for rhesus monkeys exposed by gavage, and 91 and 93 months, respectively, for rhesus monkeys exposed by intraperitoneal injection. Increased incidences of hepatocellular carcinomas were found in treated cynomolgus monkeys (5/5 compared to 0/38 in controls), rhesus monkeys exposed by gavage (6/7 compared to 0/32 in controls) and in rhesus monkeys exposed by intraperitoneal injection (3/5 compared to 0/32 in controls).

Ketkar *et al*. (1983) exposed male and female Syrian golden hamsters (30/sex/treatment group; 50/sex for controls) to 0, 0.006, 0.025 or 0.05% *N*-nitrosopiperidine in drinking water for the life of the animals. Increased incidences were noted for respiratory tract tumors (papillary polyps, papillomas and epidermoid carcinomas of the larynx, pharynx and trachea), liver tumors (hepatocellular adenomas and carcinomas, cholangiomas and cholangiocarcinomas) and digestive tract tumors (forestomach and colon adenocarcinomas). Tumor incidence data is listed in Table 3.

Table 3. *N*-Nitrosopiperidine-induced tumor induction in male and female Syrian golden hamsters (Ketkar *et al*., 1983)

Dose group (% *N*-nitrosopiperidine)	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
male		respiratory tract	
0	0		0/50
0.006	7.2		5/30
0.025	30		10/30
0.05	60		15/30
female		respiratory tract	
0	0		0/50
0.006	8.18		4/30
0.025	34.1		6/30
0.05	68.2		10/30
male		liver tumors	
0	0		0/50
0.006	7.2		1/30
0.025	30		2/30
0.05	60		10/30
female		liver tumors	
0	0		0/50
0.006	8.18		1/30
0.025	34.1		2/30
0.05	68.2		4/30
male		digestive tract	
0	0		0/50
0.006	7.2		0/30
0.025	30		4/30
0.05	60		13/30
female		digestive tract	
0	0		0/50
0.006	8.18		4/30
0.025	34.1		5/30
0.05	68.2		7/30

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al.* (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al.* (1984, 1987) list results from drinking water studies in male and female Syrian Golden hamsters, feeding studies in male ICR mice, feeding studies in rhesus and cynomolgus monkeys, intraperitoneal studies in rhesus monkeys (combined data for males and females), and drinking water studies in Sprague-Dawley rats (combined data for males and females). N-Nitrosopiperidine induced liver tumors in all species and strains. Hamsters are the least sensitive of the species tested. The majority of treated primates developed liver tumors, including all cynomolgus monkeys given the compound in feed. Rats and mice exhibit sensitivity similar to primates. Because treatment groups in the primate studies are small and incidences observed are high, accurate estimates of cancer potency cannot be obtained from these studies. Of the dose-response data available for rats and mice, the highest quality data set is reported by Eisenbrand *et al.* (1980) for liver tumors in Sprague-Dawley rats. Cancer potency is derived from this data set (Table 2) (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Analysis of the data set using the computer program TOX_RISK (Crump et al., 1991) indicated that inclusion of the high dose group resulted in a *p*-value of ≥ 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992). A unit risk factor of 6.0 E-6 $(\mu g/m^3)^{-1}$ was derived by OEHHA/ATES from the human q_1^* using an inspiration rate of 20 m^3/day.

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N-NITROSOPYRROLIDINE

CAS No: 930-55-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	100.1
Boiling point	214°C
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.10 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.0 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 2.1 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by US EPA/IRIS (1994) from rat liver tumor data (Preussmann *et al*. 1977) using a linearized multistage model]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *N*-nitrosopyrrolidine in humans are known to exist. Human exposure to nitrosamines occurs through contact with complex mixtures (e.g., metal cutting fluids) containing these compounds. US EPA (1994) states that data from such exposures are of limited use in evaluating the carcinogenicity of individual nitrosamines due to potential confounding by other substances present in the mixtures.

Animal Studies

Druckrey (1967) (reviewed by IARC, 1978) exposed 25 BD rats to drinking water containing *N*-nitrosopyrrolidine; average doses were 5 or 10 mg/kg body weight-day. After 150 days of treatment, the doses were increased to 10 or 20 mg/kg-day. Hepatocellular carcinomas were noted in 23/25 animals; the average induction time for the low- and high-dose animals was 470 and 290 days, respectively.

Male and female MRC rats (15/sex) were exposed to *N*-nitrosopyrrolidine in drinking water 5 days/week at a concentration of 200 mg/l for 67 weeks (mean total dose 1340 mg/animal, mean daily intake 16 mg/kg) (Greenblatt and Lijinsky, 1972a). After treatment, animals were observed for an additional 105 weeks. An untreated control group of 35 animals/sex was also included. An increased incidence of liver tumors (primarily hepatocellular carcinomas) were observed in both males (12/12) and females (13/13); 7/12 male rats also developed papillary mesotheliomas of the testes. No liver or testicular tumors were noted in the corresponding controls.

Greenblatt and Lijinsky (1972b) exposed male and female (30/sex/group) Swiss mice to 0 or 0.01% *N*-nitrosopyrrolidine in drinking water 5 days/week for 26 weeks (average dose 7-8 mg/kg-day). All surviving animals were killed after 38 weeks. Animals were only histopathologically evaluated for lung adenomas. Lung tumor incidence in treated mice was not significantly increased when compared to controls; however, the duration of treatment was short and the mean survival time of the treated animals was only 12 weeks, with the primary cause of mortality being liver necrosis.

Male and female Sprague-Dawley rats (14 males, 15 females) were exposed to 200 mg/l *N*-nitrosopyrrolidine in drinking water 5 days/week for 50 weeks (total dose 1000 mg/animal), then observed for the remainder of their lifetime (Lijinsky and Taylor, 1976). An increased incidence of hepatocellular tumors was noted in both males (12/14) and females (13/15). No liver tumors were reported in the control group (group size not reported).

Exposure of male and female Sprague-Dawley rats to N-nitrosopyrrolidine in drinking water at levels of 0, 0.3, 1, 3 or 10 mg/kg body weight for the life of the animals resulted in significant increases in the incidence of hepatocellular tumors (adenomas and carcinomas) (Preussmann *et al*., 1977). Tumor incidence data is listed in Table 1. Equal numbers of male and female animals were used.

Table 1: Incidence of hepatocellular carcinomas and adenomas in male and female Sprague-Dawley rats treated with *N*-nitrosopyrrolidine via drinking water (Preussmann *et al*., 1977)

Number of animals/ group[1]	*N*-nitrosopyrrolidine exposure level (mg/kg-day)	Human equivalent dose[2] (mg/kg-day)	Hepatocellular tumor incidence[1]
61	0	0	0/61
60	0.3	0.051	3/60
62	1.0	0.17	17/62
38	3.0	0.51	31/38
24	10	1.70	14/24

1. Males and females combined.
2. Calculated by US EPA (1994).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Tumor incidence data from the study by Preussmann *et al*. (1977) were the basis of cancer potency factor derivation. There were significant increases in the incidence of hepatocellular carcinomas and adenomas (see Table 1). Overall, there appeared to be dose-related increases in hepatocellular tumors, as well as shorter latency periods with increasing dose.

Methodology

Cancer potency values are based on the most sensitive site, species and study, in the absence of other evidence indicating that such a value is not appropriate (CDHS, 1985). Based on the dose-response data for hepatocellular tumors in male and female Sprague-Dawley rats, the cancer potency factor for *N*-nitrosopyrrolidine was calculated to be 2.1 $(mg/kg\text{-}day)^{-1}$ using a linearized multistage model with surface area scaling for conversion of the rat administered dose to a human equivalent dose (US EPA, 1994). A unit risk factor was calculated from the cancer potency factor by OEHHA/ATES using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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PENTACHLOROPHENOL

CAS No: 87-86-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	266.35
Boiling point	309°C
Melting point	190°C
Vapor pressure	0.00011 mm Hg @ 25°C
Air concentration conversion	1 ppm = 10.9 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.6 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 1.8 E-2 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1991) from male mouse liver tumor data (NTP, 1989) using a linearized multistage model.]

III. CARCINOGENIC EFFECTS

Human Studies

No human epidemiological studies were located that were adequate to evaluate a possible association between exposure to pentachlorophenol and cancer.

Animal Studies

The National Toxicology Program (NTP, 1989) conducted 2 studies on the carcinogenic effects of lifetime exposure of mice to pentachlorophenol (PeCP). In these studies, $B6C3F_1$ mice were exposed to dietary PeCP, as either the technical grade or EC-7 grade, for 2 years. The technical grade PeCP contained polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs) as contaminants in significantly higher concentrations than the EC-7 grade. The NTP found dose-related increases in liver and adrenal medullary tumors in male and female mice, and an increase in hemangiosarcomas in the females exposed to the EC-7 grade (Table 1). The incidence of liver neoplasms and hemangiosarcomas was higher in female mice exposed to technical grade PeCP. The incidence of hemoangiosarcomas in female mice was 0/35, 3/50, and 6/50 for the 0, 100, and 200 ppm PeCP groups, respectively.

Table 1. Tumor incidence in male and female B6C3F$_1$ mice exposed to technical or EC-7 grade pentachlorophenol (PeCP) (NTP, 1989).

Grade of PeCP	Sex	Adrenal gland/medullary tumor incidence (benign and malignant pheochromocytomas) Dietary concentration (ppm)[a] 0	100	200	600	Liver tumor incidence (hepatocellular adenomas and carcinomas) Dietary concentration (ppm)[a] 0	100	200	600
EC-7	males	1/34	4/48	21/48	45/49	6/35	19/48	21/48	34/49
	females	0/35	2/49	2/46	38/49	1/34	4/50	6/49	31/48
technical	males	0/31	10/45	23/45	NT	7/32	26/47	37/48	NT
	females	2/33	2/48	1/49	NT	3/33	9/49	9/50	NT

a) EC-7 dose levels for males and females were 0, 18, 37 and 118 mg/kg-day and 0, 17, 34 and 114 mg/kg-day, respectively.
NT = not tested

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NTP (1989) study in mice was used as the basis for the cancer potency for PeCP. This represents the only adequate, long-term, positive study of the carcinogenic effects of PeCP. The NTP study shows that PeCP exposure in mice results in several types of tumors in males and females. In the NTP (1989) study, mice (35-50 per group) were exposed to 0, 100, 200, or 600 mg/kg diet PeCP (EC-7 grade) for 2 years. In a parallel series of experiments, mice were exposed to 0, 100, or 200 mg/kg diet of technical grade PeCP. Results of these bioassays included a significant incidence of liver and adrenal neoplasms in male and female mice exposed to PeCP. In addition, female mice exhibited a significant increase in hemangiosarcomas. Although there were trace amounts of PCDD's and PCDF's in the EC-7 grade, the amount of these contaminants was determined by CHDS (1991) to be insufficient to result in the observed tumor incidence.

Methodology

A linearized multistage model was used to estimate the cancer potency of EC-7 grade PeCP from the NTP (1989) liver tumor (hepatocellular adenomas and carcinomas) data in male B6C3F$_1$ mice (Crump et al., 1982). The concentrations of PeCP given in the feed were 0, 100, 200, or 600 mg/kg diet. The tumor incidence data are shown in Table 1. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value for PeCP.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. The default lifespan for mice is 104 weeks. In this case, the lifetime scaling factor

is equal to 1. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 1.8E-2 $[mg/kg\text{-}day]^{-1}$ was derived (CDHS, 1991). An airborne unit risk factor of 4.6E-6 $(\mu g/m^3)^{-1}$ was calculated from the q_{human} value by OEHHA/ATES using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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POLYCHLORINATED BIPHENYLS (PCBs)
(≥ 60% chlorine content)

CAS No: 1336-36-3 (all congeners)

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	154 - 499
Boiling point	Unknown
Melting point	340-375° C
Vapor pressure	4.06E-4 mm Hg @ 25°C (Aroclor 1242)
	7.71E-5 mm Hg @ 25°C (Aroclor 1254)
Air concentration conversion	1 ppm = 10.87 mg/m^3 (Aroclor 1242)
	1 ppm = 13.33 mg/m^3 (Aroclor 1254)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.4 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 7.7 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

The evidence for the human carcinogenicity of PCBs has been determined by IARC (1987) to be limited, due to concurrent exposures of test subjects to other chemicals, and to the small numbers of individuals examined. A study of workers heavily exposed to Aroclor 1254 (54% chlorine, by weight) for 9 years, showed 2 out of 31 heavily exposed workers developed malignant melanoma, while 1 out of 41 less heavily exposed workers developed this tumor (Bahn *et al*., 1976; 1977). The expected number of melanomas in a population this size was 0.04. IARC (1978) concluded that there was suggestive evidence of carcinogenicity in humans.

Brown and Jones (1981) and Brown (1987) found an increase in the mortality caused by liver or biliary passage cancer (5 observed, 1.9 expected) in 2567 US workers exposed to Aroclor 1254 during the manufacture of capacitors. Four of the 5 deceased workers were female.

Bertazzi *et al*. (1982) reported on a study of capacitor manufacturing workers in Italy. Workers were exposed to mixtures of PCB congeners containing 54% chlorine prior to 1964, and 42% chlorine after that time. In these workers, significant increases in the incidence of cancers of the digestive, lymphatic, and hematopoietic systems were observed in both male and female workers. An expanded study was later conducted by Bertazzi *et al*. (1987) who recorded cancer mortality in 2100 male and female workers from 1946 to 1982. Cancers of the gastointestinal tract were significantly increased in male workers (6 observed, 2.2 expected) and hematopoietic cancers were significantly increased in female workers (4 observed, 1.1 expected).

PCB content in human fat tissues has been correlated with the occurrence of stomach, colon, pancreas, ovary, and prostate cancers (Unger *et al*., 1982; 1984).

A large population of people in Japan were exposed to PCBs from contaminated cooking oil (Umeda, 1984). In these patients, a 5-fold increase in liver cancer was reported, but a dose-response was not established. In a cohort of 887 male intoxicated patients with "Yusho" disease, Kuratsune *et al*. (1986) found an increase in mortality from malignant tumors (33 observed, 15.5 expected). Deaths from malignant liver and lung tumors were particularly high (9 observed, 1.6 expected; 8 observed, 2.5 expected, respectively). Female Yusho patients (n = 874) did not show the increase in cancer mortality.

Animal Studies

Early studies by Kimura and Baba (1973) and Ito *et al*. (1974) did not demonstrate carcinogenicity of PCBs in male or female rats orally exposed to highly chlorinated (60% by weight) PCBs in the diet for up to 77 weeks. In this study, 20 rats (10/sex) were exposed to diets ranging from 38.5 to 462 ppm PCBs. Ten rats (5/sex) served as experimental controls. Each rat was exposed to a unique treatment regimen that differed by amount of PCB ingested and duration of exposure. Female rats exhibited several benign adenomatous lesions in the liver, but no statistical comparisons were made. In these studies, small sample sizes (10 per group), less than lifetime exposure, and excess deaths unrelated to PCB exposure prevented definitive conclusions about the carcinogenicity of PCBs.

The NCI (1978) conducted a 2-year bioassay on male or female Fisher-344 rats (24 per group) exposed to Aroclor 1254 in the diet. Concentrations of PCBs in the feed were 0, 25, 50, or 100 ppm. A significant increase in the numbers of lymphomas and leukemias was observed in the male rats. The NCI did not conclude that these hematological tumors were treatment related. The incidence of hepatocarcinomas in the male rats was 0/24, 1/24, and 3/24 for the 0, 50, and 100 ppm groups, respectively. In other tissues, such as the stomach, jejunum, and cecum, rare tumors were found. The incidence of these tumors, while not statistically significant, were considered to be treatment-related due to the low incidence of these tumors in historical controls. The NCI concluded that PCBs were capable of inducing proliferative lesions in the liver, but were not carcinogenic to rats in this bioassay.

A reanalysis of the NCI data by Morgan *et al*. (1981) found that the incidence of focal metaplasia in the stomach increased in a dose-dependent fashion with a 6, 10, 17, and 35% occurrence in the 0, 25, 50, and 100 ppm groups, respectively. The incidence of stomach adenocarcinomas was significantly higher than in historical controls (4% vs. 0.03%, $p < 0.001$). With this reanalysis, the authors concluded that Aroclor 1254 was carcinogenic.

A chronic dietary exposure to Aroclor 1260 in rats was reported by Kimbrough *et al*. (1975). In this study, 200 young rats were fed 0 or 100 ppm Aroclor 1260 for 94 weeks. Actual dosages of PCB were estimated to be 11.6 mg/kg/day for the first week, 6.1 mg/kg/day at 3 months, and 4.3 mg/kg/day at 20 months. The time-weighted average dose was estimated to be

4.42 mg/kg/day (US EPA, 1985). Almost all treated rats developed liver nodules (170/184). In addition, the incidence of hepatocellular carcinomas was highly significantly increased over controls (1/173 for controls vs. 26/184 for treated rats; $p < 1.0E-6$). Neoplastic nodules and total neoplastic lesions were also highly significantly increased over concurrent controls.

Schaeffer *et al*. (1984) reported results from a 2-year bioassay in rats using 2 PCB mixtures: Clophen A 30 (30% chlorine by weight) and Clophen A 60 (60% chlorine by weight) in the diet. Groups consisted of approximately 140 male weanling rats exposed to 100 ppm of either Clophen A 30 or Clophen A 60. A significant increase in the percentage of hepatocellular carcinomas was seen in the rats treated with Clophen A 60 (62%), but not with Clophen A 30 (3%). Hepatocarcinomas were observed in 2% of control animals. Preneoplastic lesions were not observed before 71 weeks.

The incidence of hepatocarcinoma was increased in rats exposed to Aroclor 1260 in a 2-year study by Norback and Weltman (1985). In this study, 70 male or female rats were exposed to 100 ppm Aroclor 1260 in the diet for 16 months, followed by 50 ppm in the diet for 8 months. The time-weighted average doses were calculated to be 5 mg/kg/day for the male rats, and 4.2 mg/kg/day for the females. The incidence of neoplastic lesions in control rats living 18 months or longer was 1.2% (1/81). The treated rats had an incidence of 95% (45/47) for the females, and 15% (7/46) for the males. The combined tumor incidences were significantly higher in treated rats compared with controls. The authors also reported an increase in incidence of cholangiomas, but these lesions were designated by CDHS as benign, since no specific discussion of their malignancy was given.

In mice, 2 studies indicate that PCBs are carcinogenic, particularly with respect to hepatocarcinomas. Kimbrough and Linder (1974) exposed groups of 50 male Balb/cj mice to Aroclor 1254 at 0 or 300 ppm in the diet for 11 months, or for 6 months with a 5 month recovery period. The incidences of hepatoma were 0/34, and 0/24 for the 11- and 6-month exposure groups, respectively. The treated animals had incidences of 9/22, and 1/24 for the 11- and 6-month groups, respectively.

Ito *et al*. (1973) exposed groups of 12 mice to 500 ppm Kaneclor 500 (54% chlorine) in the diet for 32 weeks. No liver lesions were seen in 6 untreated controls. The incidence of hepatocellular carcinoma in the treated mice was 5/12 and the incidence of liver nodules was 7/12.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The Kimbrough *et al* (1975) study in female rats exposed to Aroclor 1260 was used by the U.S.EPA Cancer Assessment Group (CAG) in deriving the estimated human cancer potency of 4.3 $(mg/kg - day)^{-1}$ for PCBs (U.S.EPA, 1984). This value, derived using the multistage polynomial, was used in the development of the Federal Drinking Water Standard (U.S.EPA, 1987). The U.S.EPA value is based on the incidence of hepatocarcinoma and neoplastic nodules, combined. From this study, CDHS estimated the human cancer potency to be slightly lower, 4.2 $(mg/kg - day)^{-1}$, due to a correction for the length of the experiment.

A similar analysis of the Schaeffer *et al*. (1984) study in male rats exposed to Clophen A 60 would yield a human cancer potency of 1.1 $(mg/kg \times day)^{-1}$. Use of the Norbeck and Weltman (1985) study on Aroclor 1260 in male and female rats would give a slightly higher potency value of 5.0 $(mg/kg \times day)^{-1}$.

The California Guidelines for Chemical Carcinogen Risk Assessment and their Scientific Rationale (CDHS, 1985) specify that the potency value be selected from data on the most sensitive site, in the most sensitive species and study, unless evidence exists to discount such a value. From these criteria, cancer potencies from the Kimbrough (1975) or the Norbeck and Weltman (1985) studies would appear to be the most appropriate values. The two values [4.2 and 5.0 $(mg/kg - day)^{-1}$] are in close agreement with each other. Following these considerations, CDHS selected a cancer potency value of 5 $(mg/kg - day)^{-1}$ for PCBs of 60% chlorine. The various human cancer potencies derived by CHDS for PCBs are listed in Table 1.

Methodology

A linearized multistage model was used to fit the female rat carcinogenicity data from the Norback and Weltman (1985) study. The time-weighted average dose was calculated to be 4.2 mg/kg/day for the females. The assumed body weight for the female rats was 0.35 kg. The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. From the female rat data on combined tumors from Norback and Weltman (1985), the q_{animal} was calculated to be 0.81. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (rat).

A human cancer potency (q_{human}) of 5 $(mg/kg \times day)^{-1}$ was derived from the above relationships (CDHS, 1988). An airborne unit risk factor of 1.4E-3 $(\mu g/m^3)^{-1}$ was calculated from the q_{human} value by OEHHA/ATES using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

Table 1. Cancer potency values from studies on PCBs.

Species	q_{human} (mg/kg - day)$^{-1}$	Tumor type	Reference
Sprague-Dawley rats (males)	1.4×10^{-1}	trabecular carcinoma (same as combined)	Norback and Weltman (1985)
Sherman rats (female)	2.5×10^{-1}	hepatocellular carcinoma	Kimbrough *et al*. (1975)
Wistar rats (male)	1.1	hepatocellular carcinoma	Schaeffer *et al*. (1984)
Sprague-Dawley rats (females)	1.1	trabecular carcinoma	Norback and Weltman (1985)
Sprague-Dawley rats (females)	1.5	adenocarcinoma	Norback and Weltman (1985)
Sherman rats (female)	2.4	neoplastic nodules	Kimbrough *et al*. (1975)
Sherman rats (female)	4.2	combined	Kimbrough *et al*. (1975)
Sprague-Dawley rats (females)	5	combined	Norback and Weltman (1985)

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POTASSIUM BROMATE

CAS No: 7758-01-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	167.01
Boiling point	not available
Melting point	434 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 6.8 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.4 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 4.9 E-1 $(mg/kg\text{-}day)^{-1}$
[Male rat kidney tumor data (Kurokawa *et al*., 1983), contained in Gold *et al.* (1987) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of potassium bromate in humans are known to exist.

Animal Studies

Male and female Wistar rats (90/sex/group) (Fisher *et al*., 1979) and "Theiller's Original" strain mice (60/sex/group) (Ginocchio *et al*., 1979) were fed diets consisting of 79% bread crumbs made from untreated flour, or flour containing 50 mg/kg or 75 mg/kg potassium bromate. Mice and rats were fed treated diet for 80 and 104 weeks, respectively. No significant increase in tumor induction was reported; however, IARC (1986) noted that bromates are substantially degraded during bread baking.

Male and female Fischer 344 (F344) rats were exposed to 0, 250 or 500 mg/l potassium bromate in drinking water for 100 weeks (Kurokawa *et al*., 1983). Group sizes were 52-53/sex/group. Total doses were 9.6 and 21.3 mg/kg body weight for low and high dose males, respectively, and 9.6 and 19.6 mg/kg body weight for low and high dose females, respectively. Significant increases in the incidences of renal andenomas and adenocarcinomas were noted in both males and females; significant increases were also noted in the incidence of peritoneal mesotheliomas in males, and of thyroid tumors in females. Tumor incidence data is listed in Table 1.

Table 1. Potassium bromate-induced tumor incidences in male and female Fisher 344 rats (Kurokawa *et al*., 1983)

Sex	Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
male	control	0	kidney tumors[3]	3/53
	low dose	12.4		32/53
	high dose	22.5		46/52
	control	0	peritoneal mesotheliomas	6/53
	low dose	12.4		17/52
	high dose	22.5		28/46
female	control	0	kidney tumors[3]	0/47
	low dose	14.2		28/50
	high dose	28.3		39/49
	control	0	thyroid tumors	3/52
	low dose	14.2		10/52
	high dose	28.3		12/52

1. Doses as reported by Gold *et al.* (1987).
2. Tumor incidences as reported by Gold *et al.* (1987).
3. Adenomas and adenocarcinomas

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al*. (1987) list the results from positive drinking water studies in male and female F344 rats (Kurokawa *et al*., 1983) and from negative feeding studies in male and female Wistar rats (Fisher *et al*., 1979) and "Theiller's Original" mice (Ginocchio *et al*., 1979). Male and female rats are of similar sensitivity. Cancer potency is based on results from Kurokawa *et al.* (1983). The dose-response data for renal adenomas and adenocarcinomas in male rats are listed in Table 1 and are the basis for the cancer potency for potassium bromate (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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1,3-PROPANE SULTONE

CAS No: 1120-71-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	122.1
Boiling point	180°C at 30 mm Hg
Melting point	31°C
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.01 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.9 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 2.4 E+0 $(mg/kg\text{-}day)^{-1}$
[Male rat cerebellar malignant glioma tumor data (Ulland *et al*., 1971; Weisburger *et al*., 1981), contained in Gold *et al*. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992)]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 1,3-propane sultone on humans are known to exist.

Animal Studies

Several studies exist on the potential carcinogenic effects of 1,3-propane sultone in animals. These studies have been reviewed by IARC (1974).

BD rats (12/group, sex unspecified) were given 30 mg/kg body weight 1,3-propane sultone as a 3% aqueous solution weekly by gavage (Druckrey *et al*., 1970). Four of 10 survivors developed tumors between days 248 and 377; tumors noted were 1 glial-mesodermal mixed tumor, 1 advential cell sarcoma of the brain, 1 nephroblastoma and 1 subcutaneous spindle cell sarcoma.

Local sarcomas resulting in mortality were induced in all of 18 BD rats given weekly subcutaneous injections of 15 mg/kg 1,3-propane sultone in water (total dose 225 mg/kg) between 208 and 387 days. Additionally, single subcutaneous injections of 30 or 100 mg/kg produced local sarcomas at the injection site resulting in mortality in 12/18 animals and 18/18 animals, respectively (Druckrey *et al*., 1970). In the same study, BD rats were given 1,3-propane sultone as a 1% solution in arachis oil by subcutaneous injection weekly at doses of 15 or 30 mg/kg. Mortality resulted from local sarcomas which developed (myosarcomas and

fibrosarcomas) at the site of injection (7/12 and 11/11 rats in the low and high-dose groups, respectively) within 217-360 days (total dose up to 390 mg/kg) (Druckrey *et al*., 1968, 1970).

Weekly intravenous injections of a 2% solution of 1,3-propane sultone in water at doses of 10, 20 or 40 mg/kg (total doses 300, 570 and 560 mg/kg, respectively) were administered to groups of 10 BD rats (the 40 mg/kg group treatment was suspended after 16 weeks due to tail vein sclerosis) (Druckrey *et* al., 1970). Three animals in the 40 mg/kg group died of tumors after 280-410 days (sarcoma of the mediastinum with right lung and kidney metastases, glial-mesodermal mixed tumor of the brain, neurosarcoma); 2/12 and 3/8 animals respectively in the 10 and 20 mg/kg groups died of tumors (10 mg/kg group: ganglioneuroma, neurocytoma; 20 mg/kg group: nephroblastoma, ileocaecal carcinoma, glial-mesodermal mixed tumor of the brain and mammary carcinoma) after 381-492 days. In the same study, a single intravenous injection of 1,3-propane sultone (150 mg/kg) induced tumors at various sites resulting in mortality within 459 days in 10/32 BD rats. Single intravenous injections of 20 or 60 mg/kg 1,3-propane sultone administered to pregnant BD rats on gestation day 15 resulted in malignant neurogenic tumors in 3/25 offspring born to the 20 mg/kg group, and in malignant tumors in 4/14 offspring (2 neurogenic tumors, 1 pancreatic tumor, 1 ovarian tumor) born to the 60 mg/kg group.

Female ICR/Ha Swiss mice (30/group) given weekly subcutaneous injections of 0.3 mg 1,3-propane sultone in 50 µl distilled water developed tumors in 21/30 mice at the injection site (1 papilloma, 7 adenoacanthomas, 12 sarcomas, 1 undifferentiated carcinoma) within 63 weeks, compared to 0/30 controls after 78 weeks (Van Duuren *et al*., 1971).

Male and female Charles River CD rats (26/sex/group) were exposed to an aqueous solution of 1,3-propane sultone by gavage twice weekly at doses of 28 mg/kg body weight for 60 weeks and 56 mg/kg for 32 weeks (Ulland *et al*., 1971; Weisburger *et al*., 1981). Control groups (32/sex) were also included; however, only 6 animals/sex were killed and necropsied at 61 weeks. Tumor types induced by 1,3-propane sultone are listed in Table 1.

Table 1: 1,3-propane sultone-induced tumor incidences in male and female CD rats

Exposure group (mg/kg)	28		56	
Sex	Male	Female	Male	Female
Tumor type				
Breast	1/26	7/26	1/26	13/26
Glioma	12/26	15/26	16/26	13/26
Ear duct	1/26	0/26	3/26	3/26
Leukemia	0/26	2/26	4/26	3/26
Intestinal adenocarcinoma	4/26	1/26	3/26	1/26
Miscellaneous	5/26	7/26	4/26	6/26

One female control died of a cerebral glioma after 33 weeks, and a pituitary chromophobe adenoma was discovered in a female control. No other control animal tumor incidences were reported.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The carcinogenicity bioassay using male and female Charles River CD rats exposed to 1,3-propane sultone by gavage (Ulland *et al*., 1971; Weisburger *et al*., 1981) demonstrated that 1,3-propane sultone induced tumors in both sexes at multiple sites; the sensitivity of both sexes was similar. The dose-response data for cerebellar malignant glioma incidence in male rats, the most sensitive site in males, was chosen as the basis for a cancer potency factor.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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PROPYLENE OXIDE

CAS No: 75-56-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	58.08
Boiling point	34.2°C
Melting point	-112°C
Vapor pressure	543 mm Hg @ 25°C
Air concentration conversion	1 ppm = 2.37 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.7 E-6 $(\mu g/m^3)^{-1}$
[Calculated by US EPA (1995) from male rat nasal cavity hemangioma/hemangiosarcoma data (NTP,1985) using a linearized multistage procedure, extra risk.]

Oral Cancer Potency Factor: 2.4 E-1 $(mg/kg/day)^{-1}$
[Calculated by US EPA (1995) from female Sprague-Dawley rat forestomach squamous cell carcinoma tumor data (Dunkelberg, 1981), using a linearized multistage model, extra risk.]

III. CARCINOGENIC EFFECTS

Human Studies

Theiss *et al*. (1981) conducted a retrospective cohort study of 602 active and former employees who had worked for 6 months or more in one of 8 German alkylene oxide production plants. The workers had been exposed to alkylene oxides (propylene oxide and ethylene oxide) as well as to other chemicals such as dichloropropane and epichlorohydrin. No ambient propylene oxide concentrations were reported and the study included workers employed as early as 1928; propylene oxide production did not begin until 1959. No significant difference was observed between the observed and expected numbers of cancer deaths.

Animal Studies

Exposure to propylene oxide by gavage at dose levels of 0, 15 or 60 mg/kg twice weekly for 150 weeks has been shown to induce forestomach tumors (primarily squamous cell carcinomas) in female Sprague-Dawley rats (Dunkelberg, 1982). Female NMRI mice treated with 0.1, 0.3, 1.0 or 2.5 mg propylene oxide once a week for 95 weeks via subcutaneous injection demonstrated a dose-dependent increase in injection site tumors (mostly fibrosarcomas) (Dunkelberg, 1984). Subcutaneous injection of a total dose of 1500 mg/kg propylene oxide over 325 days in rats (sex and strain not specified) resulted in the induction of injection site sarcomas (8/12 and 3/12 rats

receiving propylene oxide in oil and water vehicle, respectively) (Walpole, 1958). However, the study did not include an appropriate control group.

F344 rats and $B6C3F_1$ mice (50/sex/dose) were exposed to 0, 200 or 400 ppm (0, 475 or 950 mg/m^3) of propylene oxide for 6 hours/day, 5 days/week for 102 weeks (NTP, 1985; Renne *et al*., 1986). In rats, positive trends were demonstrated for papillary adenomas of the nasal turbinate epithelium (males and females), thyroid gland C-cell adenomas or carcinomas (females) and keratoacanthomas (males). A significantly increased incidence of endometrial stromal polyps and sarcomas combined was noted for all doses. However, the NTP decided that only the nasal epithelial tumors were treatment-related because the other tumors were either relatively common (thyroid) or were of low incidence relative to historical controls. In mice, the low-dose group was killed due to an inadvertent overdose 19 weeks after the initial start date. New groups of low-dose mice of both sexes were started, but additional control groups were not included. Hemangiomas (males) and hemangiosarcomas (both sexes) were significantly increased at the high dose. One squamous cell carcinoma and one papilloma were observed in the nasal cavity of 2 high-dose males; nasal cavity adenocarcinomas were reported in 2 high-dose females. Although not statistically significant, historical controls have demonstrated an extremely low incidence of these tumor types. A significant dose-related trend and incidence of mammary gland adenocarcinomas was observed in high-dose females.

Cpb:WU Wistar rats (100/sex/group) were exposed to 0, 30, 100 or 300 ppm (0, 71, 238 or 713 mg/m^3) propylene oxide for 6 hours/day, 5 days/week for 123-124 weeks (Reuzel and Kuper, 1983; Kuper *et al.* , 1988). No nasal cavity tumors were observed; however, significant increases in degenerative changes and neoplasia of the olfactory and respiratory epithelium were noted in both sexes of all exposure groups. Significant increases were also found in mammary gland adenocarcinomas in high-dose females. Squamous-cell carcinomas of the nose, larynx/pharynx and trachea, and adenocarcinoma of the larynx/pharynx and lungs were reported in 5 high-dose males. Although not statistically significant, none of these tumor types were reported in control males.

Male F344 rats exposed to 0, 100 or 300 ppm propylene oxide for 7 hours/day, 5 days/week for 104 weeks displayed a significant increase in nasal epithelium hyperplasia in the high-dose group (Lynch *et al*., 1984). The incidence of adrenal pheochromocytomas was also increased.

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Studies by Dunkelberg (1981) and NTP (1985) demonstrated that oral and inhalation exposure, respectively, to propylene oxide can result in increased animal tumor incidence. In the study by Dunkelberg (1981), female Sprague-Dawley rats exposed to total average doses of 0, 2714 or 10,798 mg/kg-day propylene oxide for 150 weeks demonstrated a significant increase in forestomach squamous cell carcinoma tumor incidence (0/100, 2/50 and 19/50 for control, low-dose and high-dose animals, respectively). These data were used to calculate an oral cancer potency factor for propylene oxide.

In the NTP carcinogenicity study (1985), F344 rats and $B6C3F_1$ mice (50/sex/dose) were exposed to 0, 200 or 400 ppm (0, 475 or 950 mg/m^3) of propylene oxide for 6 hours/day, 5 days/week for 102 weeks. High-dose rats exhibited an increased incidence of nasal papillary adenomas (2/50 for males, 3/50 for females), suggesting a carcinogenic response. However, these increases were not significant when compared to controls (0/50 for both sexes), making them unsuitable for carcinogenicity risk estimation. The incidence of nasal cavity hemangiomas or hemangiosarcomas in mice was 10/50 and 5/50 in the high-dose males ($p = 0.001$) and females ($p = 0.028$), respectively. These data, from a study where adequate numbers of animals of both sexes were treated for a lifetime, demonstrate that inhalation exposure to propylene oxide results in respiratory tract carcinogenicity. The male rat hemangioma/hemangiosarcoma data was used as the basis for a inhalation unit risk factor.

Methodology

Oral Cancer Potency Factor

Transformed animal doses (0, 2.58 and 10.28 mg/kg/day) and human equivalent doses (0, 0.44 and 1.76 mg/kg-day) were calculated from the administered doses using a rat body weight of 0.35 kg, a human body weight of 70 kg, 1029 days as the length of the exposure, and 1050 days as the length of the experiment and animal lifespan. A human oral cancer potency factor of 1.3 E-2 $(mg/kg/day)^{-1}$ was calculated using the linearized multi-stage model developed by Kenneth Crump and adopted by US EPA (1980). US EPA has stated that the unit risk should not be used if the air concentration exceeds 3 mg/m^3, since above this concentration the unit risk may not be appropriate.

Inhalation Unit Risk Factor

Transformed animal doses (0, 55 and 110 mg/kg/day) were calculated from administered doses assuming 50% pulmonary absorption, 0.03 kg mouse body weight, 0.039 m^3/day as the daily inhalation volume for mice and an exposure duration and length of experiment of 103 weeks. The absorption factor is consistent with that observed for epichlorohydrin in rat respiratory tract (Stott and McKenna, 1984). Human equivalent doses were 0, 4.15 and 8.3 mg/kg/day. The transformed animal dose level was used to calculate an animal slope factor of 9.3E-4 $(mg/kg/day)^{-1}$ using the linearized multi-stage model developed by Kenneth Crump and adopted by US EPA (1980). A human slope factor of 1.3 E-2 $(mg/kg/day)^{-1}$ was determined using an animal body weight of 0.03 kg, a human body weight of 70 kg and an animal lifetime of 103 weeks.

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1,1,2,2-TETRACHLOROETHANE

CAS No: 79-34-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	167.9
Boiling point	146.5ºC
Melting point	-44ºC
Vapor pressure	9 mm Hg @ 30ºC
Air concentration conversion	1 ppm = 6.87 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 5.8 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 2.0 E-1 $(mg/kg\text{-}day)^{-1}$
[Calculated by US EPA from NCI (1978) female mouse hepatocellular carcinoma tumor data using a linearized multistage model, extra risk]

III. CARCINOGENIC EFFECTS

Human Studies

Norman *et al*. (1981) studied Army personnel assigned to treat chemical warfare protective equipment with material dissolved in tetrachloroethane. Of 3859 workers assigned to this process, 1099 whites and 124 blacks had probable exposure to the solvent. No statistically significant excess cancer mortality was noted. Slight excesses were noted for leukemia (SMR = 272, based on 4 deaths) and cancer of the genital organs (SMR = 158, based on 3 deaths).

Animal Studies

Theiss *et al*. (1977) exposed groups of 20 male A/st mice to 1,1,2,2-tetrachloroethane in tricaprylin by intraperitoneal injection (3/week) at doses of 80 mg/kg body weight, 200 mg/kg or 400 mg/kg. All survivors (10, 15 and 5 at the three doses, respectively) were killed 24 weeks after the first injection. The average number of tumors/animal were not significantly increased in the treated mice (0.3, 0.5 and 1.0 at the three doses, respectively compared to 0.27 for controls). However, the poor survival of treated animals and inadequate length of observation made this study unusable for a determination of the carcinogenicity of 1,1,2,2-tetrachloroethane.

$B6C3F_1$ mice (50 male, 50 female) were treated with technical grade (90% pure) 1,1,2,2-tetrachloroethane in corn oil by gavage 5 days/week (NCI, 1978). Low-dose and high-dose mice initially received 100 and 200 mg/kg body weight/day, respectively. Doses were increased to 150 and 300 mg/kg respectively at 18 weeks, 200 and 400 mg/kg at 21 weeks and 150 and 300

mg/kg at 26 weeks. Total duration of exposure was 78 weeks. Animals were killed 12 weeks after exposure termination. The low and high time-weighted average doses for males and females was 142 and 282 mg/kg/day, respectively. Control groups (20 male, 20 female) were left untreated or given corn oil alone for 78 weeks, and were then killed after 90 weeks. Only 1 high-dose male survived to 90 weeks, compared with 34% of the females. The incidence of hepatocellular carcinoma was positively correlated with dose level ($p<0.001$) in both male and female mice; tumor incidence in males was 1/18 for vehicle-treated controls, 13/50 for the low-dose group and 44/49 for the high-dose group. The respective tumor incidence for females was 0/19, 30/48 and 43/47.

Osborne-Mendel rats (50 male, 50 female) were treated with technical grade 1,1,2,2-tetra-chloroethane in corn oil by gavage 5 days/week (NCI, 1978). High-dose animals initially received 100 mg/kg body weight/day. In males, doses were increased to 130 mg/kg at 14 weeks, followed by 9 cycles of 4 weeks at 130 mg/kg followed by 1 week treatment-free starting at 32 weeks. In females, the dose was reduced at 25 weeks to 80 mg/kg, then followed at 32 weeks by the cyclic dosing protocol described for males (dose level 80 mg/kg). The duration of the cyclic dosing for both males and females was 45 weeks. Low-dose rats were initially exposed to 50 mg/kg/day. Doses were increased for males to 65 mg/kg at 14 weeks; doses were decreased for females to 40 mg/kg at 25 weeks. The total duration of exposure for both dose groups was 78 weeks, followed by 32 weeks without treatment. The low and high time-weighted average doses were 62 and 108 mg/kg/day for males and 43 and 76 mg/kg/day for females. Control groups (20 male, 20 female) were left untreated or given corn oil alone for 78 weeks; all surviving control and exposed animals were killed at 110 weeks. No significant increases in tumor incidence for any tumor type were noted in exposed animals. However, 2 of 49 high-dose males developed hepatocellular carcinomas and another developed a neoplastic nodule, compared with 0/20 vehicle controls.

Detailed reviews of these studies have been performed by IARC (1979) and US EPA (1980).

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Data from the bioassay of 1,1,2,2-tetrachloroethane by NCI (1978) was selected as the basis of a cancer potency factor because it demonstrated a dose-responsive induction of carcinogenicity after exposure to 1,1,2,2-tetrachloroethane in both sexes of a susceptible species ($B6C3F_1$ mice). Tumor incidence data from the most sensitive sex was used (hepatocellular carcinomas in females).

Methodology

The linearized multi-stage model developed by Kenneth Crump and adopted by US EPA (1980) was used to calculate a slope factor of 2.0 E-1 $(mg/kg/day)^{-1}$ from the NCI (1978) female $B6C3F_1$ mouse hepatocellular carcinoma incidence data. Calculation of the unit risk from the slope factor assumed a body weight of 70 kg and an inspiration rate of 20 m^3/day.

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THIOACETAMIDE

CAS No: 62-55-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	75.14
Boiling point	not available
Melting point	113-114 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 3.1 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.7 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 6.1 E+1 $(mg/kg\text{-}day)^{-1}$
[Female mouse liver tumor data (Gothoskar *et al.*, 1970), contained in Gold *et al*. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of thioacetamide in humans are known to exist.

Animal Studies

Male albino rats (10/group) were exposed to thioacetamide in the diet for 18 months (Fitzhugh and Nelson, 1948). Dietary thioacetamide levels were 0, 50, 100, 250, 500 or 1000 mg/kg diet. Animals exposed to 1000 mg/kg diet thioacetamide survived for less than one month; animals exposed to 250 or 500 mg/kg diet thioacetamide also had increased mortality. One animal in the 500 mg/kg diet exposure group developed a hepatocellular carcinoma (the number of surviving animals in this group was unspecified). One animal of the 6 survivors in the 50 and 100 mg/kg diet exposure groups developed a hepatocellular adenoma. No liver tumors were observed in the control animals.

Gupta (1955, 1956) exposed 150 male and female Wistar rats to 32 mg/kg diet thioacetamide in the diet for more than 23 weeks; an untreated control group of 50 animals was included in the study. Bile duct tumors (unspecified type) were observed in 18/36 animals killed between 9 and 23 weeks; no liver tumors were noted in the control animals. Liver tumor metastases to the ovaries were noted in 4/5 animals treated for 47 weeks or longer.

Male and female Swiss mice were fed diet containing 0.03% thioacetamide for 65 weeks (89 mice total); an untreated control group was included in the study (Gothoskar *et al*., 1970).

Interim sacrifices were performed at 6, 9 and 13 months. An increased incidence of liver tumors (hepatomas) was noted in both males and females. Tumor incidence data is listed in Table 1.

Table 1. Thioacetamide-induced hepatoma incidence in male and female Swiss mice (Gothoskar *et al*., 1970)

Dose group	Average dose[1] (mg/kg-day)	Tumor incidence
male control	0	0/6
male treated	36	6/6
female control	0	0/6
female treated	39	6/7

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al.* (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al.* (1984) list results from the study of thioacetamide by Gothoskar *et al.* (1970) in male and female Swiss mice. A total of 89 mice of both sexes were fed a diet containing 0.03% thioacetamide for 6, 9, 13 or 17 months. The group studied for 17 months consisted of 12 control mice (6 male and 6 female) and 13 treated mice (6 male and 7 female). Hepatomas were seen in all treated male mice, precluding estimation of the upper bound on potency in these animals. Females were slightly less sensitive; six of the seven dosed female mice developed hepatomas. Because this is the only dose-response data available in Gold *et al*., the data for the females are used to derive potency (see Table 1). The value presented here may be an underestimate, but is the best value currently available (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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TOLUENE DIISOCYANATE
CAS No: 26471-62-5

2,4-TOLUENE DIISOCYANATE
CAS No: 584-84-9

2,6-TOLUENE DIISOCYANATE
CAS No: 91-08-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	174.15
Boiling point	251°C at 760 mm Hg
Freezing point	22°C (pure toluene-2,4-diisocyanate (IARC, 1985); 7.2°C (pure toluene-2,6-diisocyanate (IARC, 1985)
Vapor pressure	0.01 mm Hg at 20°C
Air concentration conversion	1 ppm = 7.12 mg/m^3 (IARC, 1985)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 3.9 E-2 $(mg/kg\text{-}day)^{-1}$
[Male rat subcutaneous fibroma/fibrosarcoma tumor data (NTP, 1986) contained in Gold *et* al. database (1990), expedited Proposition 65 methodology (Cal/EPA, 1992)]

III. CARCINOGENIC EFFECTS

Human Studies

No epidemiological studies examining potential carcinogenic effects of 2,4- and 2,6-toluene-diisocyanate (TDI) on humans are known to exist. A case report reviewed by IARC (1985) described a 47-year old nonsmoking spray painter with a lung adenocarcinoma who had been exposed to TDI and 4,4'-methylenediphenyl diisocyanate for 15 years and had a 10-year history of lung disease thought to be caused by isocyanate exposure (Mortillaro and Schiavon, 1982).

Animal Studies

The National Toxicology Program (NTP) (1986) exposed male and female Fischer 344 344/N rats and $B6C3F_1$ mice (50/sex/exposure group) to commercial grade TDI (86% 2,4 isomer; 14% 2,6 isomer) in corn oil by gavage 5 days/week for 106 and 105 weeks, respectively. Rat exposure groups were 30 or 60 mg/kg for males and 60 or 120 mg/kg for females. Mouse exposure groups were 120 or 240 mg/kg body weight for males and 60 or 120 mg/kg for females. Vehicle control groups (50/sex/species) were included.

A dose-dependent reduction in survival occurred in treated rats; 36/50 (72%) controls, 14/50 (28%) low-dose and 8/50 (16%) high-dose males, and 36/50 (72%) controls, 19/50 (38%) low-dose and 6/50 (12%) high-dose females survived to study termination (108 weeks). A treatment-related induction of subcutaneous fibromas and fibrosarcomas was noted in males and females. The combined fibroma/fibrosarcoma incidence was 3/50 (6%) in controls, 6/50 (12%) in low-dose and 12/50 (24%) in high-dose males, and 2/50 (4%) in controls, 1/50 (2%) in low-dose and 5/50 (10%) in high-dose females. Fibromas and fibromasarcomas occurred in male and female rats with a statistically positive trend, and the incidence in both high-dose males and females was significantly greater than controls. Increased mammary gland tumor incidence in female rats was found to be significant in both the low- and high-dose groups by life table and incidental tumor analysis. The first mammary tumor was seen in an animal dying at week 84; the survival-adjusted mammary tumor incidences were 17/45 (38%) for controls, 25/36 (69%) for low-dose and 21/28 (75%) for high-dose animals. Increased incidences of pancreatic acinar cell adenomas with a statistically significant trend were observed in male rats; the incidence in the high-dose group was significantly greater than that in the controls. Pancreatic acinar nodular hyperplasia incidence was also increased in male rats in a dose-dependent manner (control, 0%; low-dose, 4%; high-dose, 8%). A statistically significant trend was noted for pancreatic islet cell adenoma incidence in both male and female rats; the incidences were significantly greater than those in the controls in both dose groups for females, and in the high-dose group for males. A significant dose-related increase in hepatic neoplastic nodule incidence in high-dose female rats was also noted.

Survival of high-dose male mice was reduced; 26/50 (52%) animals in this group were still alive at study termination (week 107) compared to 46/50 (92%) controls and 40/50 (80%) in the low-dose group. No statistically significant increase in tumor incidence was noted in treated male mice. A statistically significant positive trend was observed in the incidence of hemangiomas and hemangiosarcomas (in liver, ovaries or peritoneum), lymphomas, and hepatocellular adenomas and carcinomas in female mice. Overall hemangioma and hemangiosarcoma incidence was 0/50 in controls, 1/50 (2%) in the low-dose group and 5/50 (10%) in the high-dose group. Pairwise comparisons between the control and high-dose groups also indicated a significantly increased tumor incidence in the high-dose group. Combined hepatocellular adenoma and carcinoma incidence was 4/50 (8%) in controls, 5/50 (10%) in the low-dose group and 15/50 (30%) in the high-dose group. Tumor incidence in the high-dose group was significantly greater than in the controls. Overall lymphoma incidence was 10/50 (20%) in controls, 17/50 (34%) in the low-dose group, and 16/50 (32%) in the high-dose group; high-dose group tumor incidence was significantly greater than controls.

Male and female CD-1 mice and Sprague-Dawley CD rats (120/sex/group) were exposed to 0, 0.05 or 0.15 ppm (0, 0.36 or 1.07 mg/m^3) industrial-grade TDI (approximately 80% 2,4 isomer, 20% 2,6 isomer) by inhalation for 6 hours/day, 5 days/week, for 104 (mice), 108 (female rats) or 110 (male rats) weeks (Loeser, 1983). No treatment-induced increase in tumor incidence was noted in rats or mice. However, the rat histopathological evaluation was incomplete. Also, NTP (1986) noted that the exposure levels used corresponded to daily gavage doses of less than 1 mg/kg, and may not have been adequate doses to detect a potential carcinogenic response.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NTP carcinogenicity study (1986) demonstrated that TDI induced tumors in several species (rats and mice), in both sexes in at least one of those species, at multiple sites. The male rat subcutaneous fibroma/fibrosarcoma tumor data was chosen as the basis of a cancer potency factor because it was the most sensitive endpoint in the most sensitive of the responsive species and sexes tested.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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1,1,2-TRICHLOROETHANE (Vinyl trichloride)

CAS No: 79-00-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1995) except as noted)

Molecular weight	133.42
Boiling point	113.8°C at 760 mm Hg
Melting point	-36.5°C
Vapor pressure	23 mm Hg at 25°C
Air concentration conversion	1 ppm = 5.55 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.1 E-5 $(\mu g/m^3)^{-1}$
[Calculated by US EPA/IRIS (1980, 1994) from male mouse hepatocellular carcinoma tumor data (NCI, 1978), using a linearized multistage model, extra risk.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 1,1,2-trichloroethane in humans are known to exist.

Animal Studies

The carcinogenicity of 1,1,2-trichloroethane in rats and mice was studied by the National Cancer Institute (NCI, 1978). Groups of 50 male and female $B6C3F_1$ mice (5 weeks of age) and Osborne-Mendel rats (6 weeks of age) were exposed to technical-grade 1,1,2-trichloroethane (92.7% pure, impurities unspecified) by gavage on 5 consecutive days/week for 78 weeks of a 90-91 week (mice) or 111-113 week (rats) experimental period.

Low and high dose mice received 150 and 300 mg/kg body weight, respectively, for 8 weeks, followed by 200 and 400 mg/kg, respectively, for 70 weeks, followed by 12-13 weeks without treatment, after which the experiment was terminated. The time-weighted average doses were 195 and 390 mg/kg, respectively. Untreated control and vehicle control groups were included (20 animals/sex/group).

Low and high dose rats received 35 and 70 mg/kg body weight, respectively, for 20 weeks, followed by 50 and 100 mg/kg, respectively, for 58 weeks, followed by 34-35 weeks without treatment, after which the experiment was terminated. The time-weighted average doses were 46 and 92 mg/kg, respectively. Untreated control and vehicle control groups were included (20 animals/sex/group).

No statistically significant increase in 1,1,2-trichloroethane-induced tumor incidence was noted in either male or female rats. Increases in hepatocellular carcinoma incidence were noted in all male and female mouse 1,1,2-trichloroethane-exposed treatment groups. The Fisher exact test comparing tumor incidences of dosed to control groups and the Cochran-Armitage test for positive dose-related trend indicated a highly significant association ($p < 0.001$) between hepatocellular carcinomas and 1,1,2-trichloroethane exposure. A positive dose-related association between 1,1,2-trichloroethane exposure and adrenal gland pheochromocytoma incidence in male and female mice was also indicated by the Cochran-Armitage test ($p = 0.003$ for males, $p < 0.001$ for females). Fisher exact tests confirmed these results for high dose female mice ($p = 0.006$) but not for other mouse treatment groups. Mouse tumor incidence data is listed in Table 1.

Table 1. 1,1,2-Trichloroethane-induced $B6C3F_1$ mouse tumor incidence data (NCI, 1978)

Treatment group[1] (mg/kg/day)	Time-weighted[2] average dose (mg/kg/day)	Human equivalent dose[2] (mg/kg/day)	Tumor incidence[3]
			hepatocellular carcinomas
males			
vehicle control	0	0	2/20
low dose	139	9.3	18/49
high dose	279	18.6	37/49
females			
vehicle control	0	0	0/20
low dose	139	9.3	16/48
high dose	279	18.6	40/45

1. Low and high doses: 150 and 300 mg/kg body weight, respectively, for 8 weeks, followed by 200 and 400 mg/kg, respectively, for 70 weeks, followed by 12-13 weeks without treatment.
2. Doses as reported by US EPA (1994).
3. Tumor incidences as reported by US EPA (1994).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NCI (1978) carcinogenicity bioassay of 1,1,2-trichloroethane indicated that 1,1,2-trichloroethane induced tumor formation in male and female $B6C3F_1$ mice. The cancer potency value is based on the dose-response data for hepatocellular carcinomas in male mice.

Methodology

Doses are time-weighted averages adjusted for frequency of exposure (5 of 7 days/week) (US EPA, 1994). Weight of the mice was assumed to be 0.033 kg. A linearized multistage model was used to calculate a slope factor of 1.7 E+1 $(mg/kg/day)^{-1}$ and a unit risk value of 1.6 E-5 $(\mu g/m^3)^{-1}$ from the NCI (1978) male mouse hepatocellular carcinoma incidence data.

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2,4,6-TRICHLOROPHENOL

CAS No: 88-06-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	197.5
Boiling point	246°C
Melting point	69°C
Vapor pressure	0.012 mm Hg @ 25°C
Air concentration conversion	1 ppm = 8.00 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.0 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 7.0 E-2 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There are no human carcinogenicity studies available for 2,4,6-trichlorophenol.

Animal Studies

Innes *et al.* (1969) administered 100 mg/kg body weight 2,4,6-trichlorophenol by oral gavage to two F_1 generation strains of mice, $B6C3F_1$ (C57BL/6 × C3H/Anf) and $B6AKF_1$ (C57BL/6 × AKH) (18/sex/strain) from day 7 to 28 of life, without adjusting the initial dose to account for weight gain. After 28 days, 2,4,6-trichlorophenol was added to feed at 260 ppm for 74 weeks. Surviving animals were sacrificed at 78 weeks. Survival data and tumor incidence are reported in Table 1. Incidence of tumors of all types was found to be significantly increased only among treated $B6C3F_1$ males (p=0.004; Fisher's exact test). Incidence of reticulum cell tumors was also found to be significantly increased among pooled male and female treated $B6C3F_1$ animals (p=0.005). Pairwise comparison of summary incidence data shows an increased incidence of hepatomas among treated $B6C3F_1$ females (p=0.028) and reticulum cell sarcomas among treated $B6C3F_1$ males (p=0.021). Some results of this study were published separately (Bionetics Research Laboratories, 1968).

A lifetime feeding study of 2,4,6-trichlorophenol was conducted by the National Cancer Institute in two species, $B6C3F_1$ mice and F344 rats (NCI, 1979). Rats (50/sex/group) were treated with 5,000 or 10,000 ppm 2,4,6-trichlorophenol in feed for 106-107 weeks, plus a control group of 20

rats/sex given only standard feed. Tumor incidence data are presented in Table 2. Significant increases in hematopoietic tumor (malignant lymphoma and monocytic leukemia) incidence was observed among males of both the low-dose (p=0.013) and high-dose (p=0.002) groups.

In the same study (NCI, 1979), $B6C3F_1$ mice were treated with 2,4,6-trichlorophenol in feed for 105 weeks. Male mice (50/group) were treated with 5,000 or 10,000 ppm 2,4,6-trichlorophenol. Female mice (50/group) were initially treated with diets containing 10,000 and 20,000 ppm 2,4,6-trichlorophenol; however, indications of reduced growth rate at 38 weeks led the investigators to reduce the level of compound to 2,500 and 5,000 ppm 2,4,6-trichlorophenol for the balance of the experiment, leading to time-weighted average concentrations of 5,214 and 10,428 ppm. The control group consisted of mice (20/sex) given the standard diet. Tumor incidence data are presented in Table 3. A significant increase in hepatoma incidence was observed among male mice in both treatment groups and among female mice in the high dose group ($p<0.001$, Fisher's exact test).

In an effort to establish whether 2,4,6-trichlorophenol may be acting as a tumor initiator, Bull *et al.* (1986) treated female SENCAR mice (30/group) with 200 mg/kg 2,4,6-trichlorophenol by several routes of exposure, including gavage, intraperitoneal injection, subcutaneous injection, and dermal application, followed by dermal application of 1.0 μg 12-o-tetradecanoylphorbol-13-acetate three time per week for 20 weeks. No skin tumors were found when survivors were examined 52 weeks after first exposure.

Table 1. Survival and tumor incidence in male and female $B6AKF_1$ and $B6C3F_1$ mice treated with 2,4,6-trichlorophenol (Innes *et al*., 1969).

		tumor incidence				
		$B6C3F_1$			$B6AKF_1$	
tumor type	treatment[1]	total	male	female	male	female
total tumors	treated	16/36	9/18[2]	7/18[3]	3/17	2/17
	control	30/166	22/79	8/87	16/90	7/82
hepatomas	treated	5/36[4]	3/18	2/18[5]	1/18	1/18
	control	17/166	17/79	0/87		
reticulum cell sarcomas	treated	6/36[6]	4/18[7]	2/18	0/18	1/18
	control	5/166	3/79	2/87		

[1] $B6C3F_1$ and $B6AKF_1$ mice were treated with 100 mg/kg body weight 2,4,6-trichlorophenol by oral gavage from day 7 to 28 of life, then fed diet containing 260 ppm 2,4,6-trichlorophenol for 74 weeks, at which time surviving animals were sacrificed.
[2] p = 0.064, Fisher's exact test.
[3] p = 0.004, Fisher's exact test.
[4] p = 0.059, Fisher's exact test.
[5] p = 0.028, pairwise comparison of summary incidence data.
[6] p = 0.005, Fisher's exact test.
[7] p = 0.021, pairwise comparison of summary incidence data.

Table 2. Tumor incidence in Fischer F344 rats treated with 2,4,6-trichlorophenol (NCI, 1979).

tumor type/ treatment[1]		tumor incidence	
		male	female
total hemato-poietic tumors	control	4/20	3/20
	low-dose	25/50[2]	11/50
	high-dose	29/50[3]	13/50
malignant lymphoma	control	1/20	0/20
	low-dose	2/50	0/50
	high-dose	0/50	2/50
monocytic leukemia	control	3/20	3/20
	low-dose	23/50[4]	11/50
	high-dose	29/50[5]	11/50

[1] F344 rats were treated with diet containing 5,000 or 10,000 ppm 2,4,6-trichlorophenol for 106-107 weeks at which time animals were sacrificed.
[2] $p = 0.019$, Fisher's exact test.
[3] $p = 0.004$, Fisher's exact test.
[4] $p = 0.013$, Fisher's exact test.
[5] $p = 0.002$, Fisher's exact test

Table 3. Hepatoma incidence in $B6C3F_1$ mice treated with 2,4,6-trichlorophenol (NCI, 1979).

treatment[1]/hepatoma type		tumor incidence	
		male	female
control	adenoma	3/20	1/20
	carcinoma	1/20	0/20
	total	4/20	1/20
low-dose	adenoma	22/49	12/50
	carcinoma	10/49	0/50
	total	32/49[2]	12/50[3]
high-dose	adenoma	32/47	17/48
	carcinoma	7/47	7/48
	total	39/47[2]	24/48[2]

[1] Male $B6C3F_1$ mice were treated with diet containing 5,000 or 10,000 ppm 2,4,6-trichlorophenol for 105 weeks, then sacrificed. Female $B6C3F_1$ mice were treated with diet containing 10,000 or 20,000 ppm 2,4,6-trichlorophenol for 38 weeks at which time diet concentrations were reduced to 2,500 or 5,000 ppm 2,4,6-trichlorophenol, respectively, until they were sacrificed at 105 weeks.
[2] $p < 0.001$, Fisher's exact test.
[3] $p = 0.059$, Fisher's exact test.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Two studies, Innes *et al.* (1969) and NCI (1979), have been deemed adequate for the derivation of cancer potencies. Both demonstrate statistically significant increases in tumor incidence among 2,4,6-trichlorophenol exposed animal populations. Innes *et al.* (1969) show increased incidence of reticulum cell sarcomas in male $B6C3F_1$ mice and heptomas in female $B6C3F_1$ mice. The NCI (1979) study shows increased incidence of hepatomas in both male and female $B6C3F_1$ mice, and leukemia in male Fischer F344 rats. The US EPA estimate of cancer potency of 2,4,6-trichlorophenol derived from the rat study is lower than that for mice (US EPA, 1988 and below). Since selection of the potency value is made on the basis of the most sensitive species, site, and study in the absence of evidence that the data are not representative, tumor induction in $B6C3F_1$ mice has been chosen as the basis for derivation of a cancer potency value for 2,4,6-trichlorophenol.

Methodology

The multistage Doll-Armitage model polynomial was fit to tumor incidence data from Innes *et al.*(1969) and NCI (1979) (Armitage and Doll, 1954). Dosage estimates for the studies were based on food intake assumptions of 12% and 13% of body weight for male and female mice, respectively (Gold, 1984). In the NCI (1979) study, final dose values were calculated to be 1200 and 600 mg/kg-day for high- and low-dose females, and 1356 and 678 mg/kg-day for high- and low-dose males. In the Innes *et al.*(1969) study, dosage estimates were based on the method of Crouch to account for variation in dosing during the course of the experiment (Crouch, 1983). Dosage estimates were calculated to be 32.5 and 34.7 mg/kg-day for male and female mice, respectively. Using a multistage polynomial, the cancer potency was derived using the probability of dying with a tumor from a given dose and the background lifetime cancer incidence (Crump and Howe, 1984). The upper 95% confidence bound on the cancer potency was termed q_1^*. Estimates of q_1^* for tumor induction in $B6C3F_1$ mice are presented in Table 4.

Calculation of the cancer potency in animals (q_{animal}) can be made using q_1^* and the following relationship, where T is the natural lifespan of the animal (104 weeks) and T_e is the experimental duration (Innes *et al.*, T_e = 104 weeks; NCI, T_e = 78 weeks):

$$q_{animal} = q_1^* \times (T/T_e)^3$$

The resulting q_{animal} can be converted to human cancer potency (q_{human}) based on the following relationship, where bw_{animal} is the assumed body weight for the test species (Innes *et al.* (1969), bw_{animal} = 0.030 kg; NCI (1979), bw_{animal} = 0.04 kg-males and 0.035 kg-females) and bw_{human} is the assumed human body weight (70 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

Table 4. Derivation of cancer potencies from NCI (1979) and Innes *et al.*(1969).

study	tumor/group	q_1^* $(mg/kg\text{-}day)^{-1}$	q_{animal} $(mg/kg\text{-}day)^{-1}$	q_{human} $(mg/kg\text{-}day)^{-1}$	maximum likelihood estimate	LCB (95%)
NCI, 1979	hepatoma/ male	0.0017	12.1	0.021	0.016	0.004
	hepatoma/ female	0.0006	12.6	0.008	0.003	0
Innes, 1969	reticulum cell sarcoma/ male	0.035	0.035	0.47	0.2	0.05
	hepatoma/ female	0.021	0.021	0.28	0.11	0.03

LCB = Lower confidence bound.

The highest upper bound cancer potency for humans (q_{human}) was derived from the results of the Innes *et al.* (1969) study showing reticulum cell tumor induction in male $B6C3F_1$ mice. However, confidence in this value is reduced because the number of animals used in the study is small (18/group) and data were reported incompletely. Innes *et al.* (1969) and NCI (1979) both present data showing induction of hepatomas in female $B6C3F_1$ mice. However, lack of overlap between the 95% confidence bounds of the two potencies suggests there may be a greater sensitivity to this effect in the strain used by Innes *et al* (1969). Selection of a cancer potency value is made based on the most sensitive species, site, and study in the absence of evidence indicating the value is not representative (CDHS, 1985). On balance, the evidence favors neither the higher sensitivity of the Innes *et al.* (1969) study nor the high quality of the NCI (1979) study. For this reason, a method of Anderson (1983) was chosen for combining the results of these studies. The resulting cancer potency derived from the geometric mean of the four potencies shown in Table 4 is 0.07 $(mg/kg\text{-}day)^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.0 E-5 $(\mu g/m^3)^{-1}$.

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URETHANE

CAS No: 51-79-6

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	89.09
Boiling point	182-184°C
Melting point	48-50°C
Vapor pressure	0.36 mm Hg @ 25°C
Air concentration conversion	1 ppm = 3.64 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.9 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.0 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a potency factor derived by RCHAS/OEHHA (CDHS, 1989)]

III. CARCINOGENIC EFFECTS

Human Studies

There are no studies available directly linking urethane exposure to induction of cancer in humans. Urethane is, however, frequently present in alcoholic beverages, particularly brandy, whisky and wine, and IARC has recognized alcoholic beverages as carcinogenic to humans (IARC, 1988). Although other compounds present in alcoholic beverages may account for this effect, urethane may be a contributor to alcohol-related increases in cancer incidence.

Animal Studies

CDHS (1989) has identified nearly 200 studies which demonstrate the carcinogenicity of urethane in animals. Below are summaries of those determined to be most relevant in the establishment of the reference cancer potency value, with emphasis on studies performed by realistic routes of exposure and in multiple doses.

Pietra and Shubik (1960) exposed male and female Syrian golden hamsters (10/sex) to drinking water containing 0.2% urethane for life. Control animals (49 male and 14 female) received plain drinking water. Animals were autopsied at death. Among exposed animals, males showed increased incidence of dermal melanotic tumors (7/10 exposed, 1/49 control; $p < 0.01$, Fisher's exact test). Male and female animals showed an increased incidence of forestomach papillomas (males: 4/10 exposed, 0/49 control; females: 6/10 exposed, 0/14 control; $p < 0.01$). Other tumors

noted in exposed animals but not control animals include single cases of thyroid adenoma and liver hemangiosarcoma in males, malignant lymphoma and bronchial adenoma in females.
Toth *et al.* (1961a) exposed Syrian golden hamsters (31 male; 30 female) to drinking water containing 0.2% urethane. Control groups of 54 male and 47 female received plain drinking water. Dosing began at 5 weeks and continued to 25 weeks at which point the drinking water urethane concentration was increased to 0.4%. At 40 weeks treatment was discontinued due to diarrhea among the animals. At 48 weeks, treatment with 0.4% urethane resumed, but was discontinued permanently at 50 weeks due to diarrhea. Survival was significantly decreased in exposed male and female hamsters. Among exposed animals, significant increases in incidence of dermal melanotic tumors (12/27 exposed males vs. 0/54 control males; 11/25 exposed females vs. 0/47 control females; $p \leq 10^{-6}$; Fisher's exact test), forestomach papillomas (22/27 exposed vs. 0/54 control, $p < 10^{-15}$, males; 18/25 exposed vs. 1/47 control; $p < 10^{-9}$, females) and carcinomas (3/27 exposed vs. 0/54 control; $p = 0.04$, males; 2/25 exposed vs. 0/47 control; $p = 0.1$, females), pulmonary adenomatosis (3/27 exposed vs. 0/54 control; $p = 0.04$, males), mammary tumors (3/25 exposed vs. 0/47 control; $p = 0.04$, females), hepatomas (3/27 exposed vs. 0/54 control; $p = 0.04$, males), and hepatic or splenic hemangiomas (5/27 exposed vs. 0/54 control; $p = 0.04$, males) were found.

Toth and Boreisha (1969) exposed Syrian golden hamsters (48 male and 52 female) to drinking water containing 0.1% urethane for life, beginning at 5 weeks of age. Control groups (100/sex) received plain drinking water. Survival was significantly decreased in exposed male and female animals. An increased incidence of dermal melanocytosis (26/49 exposed males vs. 1/88 control males; 25/41 exposed females vs. 0/79 control females; $p = 10^{-14}$; Fisher's exact test), forestomach papillomas (36/49 exposed vs. 6/88 control, $p = 10^{-15}$, males; 35/44 exposed vs. 2/84 control, $p = 10^{-20}$, females) and adenomatous polyps of the cecum (4/40 exposed vs. 0/79 control, $p = 0.01$, males; 7/33 exposed vs. 0/72 control, $p = 0.001$, females) was noted in both males and female animals. Among females an increased incidence of gall bladder papillomas, adrenal cortex carcinomas, thyroid carcinomas, ovarian carcinomas, vaginal carcinomas, and lung adenomatosis was observed ($p < 0.05$). Hemangiosarcoma incidence was increased in exposed males.

Tannenbaum *et al.* (1962) exposed Sprague-Dawley rats (15/group) to drinking water containing 0.1% urethane. Two "young" groups, one virgin females and the other males, were treated from age 7 weeks to 32 weeks. A third group of virgin females was treated for 14 weeks from age 32 weeks. Age and sex matched control groups of 15 each receiving plain drinking water were included in the study. Animals were autopsied at the time of natural death unless sacrificed when moribund. Survival was reduced in the treated groups. Incidence of Zymbal gland carcinoma was increased in treated "young" male rats (4/15 treated vs. 0/15 control, $p = 0.05$, Fisher's exact test) and female rats (3/15 treated vs. 0/15 control, $p = 0.11$). Control animals showed higher incidence of mammary tumors than treated animals, most likely because of the reduced survival of treated animals. Tumors noted among treated animals, but not control animals, include malignant lymphoma, sarcoma, and kidney tumors.

Schmähl *et al.* (1977) and Port (1976) report on exposure of rats and mice to urethane in drinking water. Tumor specific incidence data are reported by Port (1985). Male and female NMRI mice

and Sprague-Dawley rats (40/sex/group) were exposed to urethane in drinking water from 8 weeks of age for their lifetime such that the daily dose rate was 0, 0.1, 0.5, 2.5, or 12.5 mg/kg body weight. Animals were given the appropriate dose in 20 ml drinking water. Animals were observed until their natural death. Among mice, significant increases in tumor incidence ($p < 0.1$ by Fisher's exact test) were found for pulmonary adenoma in males (6/40, 9/40, 14/40 in the 0.5, 2.5, and 12.5 mg/kg dose groups, respectively vs. 0/40 controls), and pulmonary adenoma (12/40 treated with 12.5 mg/kg urethane vs. 5/40 controls), pulmonary carcinoma (5/40 treated with 12.5 mg/kg urethane vs. 0/40 controls), angiosarcoma of the liver (4/40 treated with 12.5 mg/kg urethane vs. 0/40 controls), and mammary carcinoma (4/40 treated with 12.5 mg/kg urethane vs. 0/40 controls) in females. For each of these tumor types, the trend toward increased incidence was found to be dose-related ($p < 0.01$ by Mantel-Haenszel trend test). Among female rats, a significant increase in the incidence of mammary carcinoma (1/40, 2/40, 9/40 in the 0.5, 2.5, and 12.5 mg/kg urethane dose groups, respectively vs. 0/40 in the 0.1 mg/kg urethane dose group, $p = 0.0011$) and the combined incidence of mammary adenoma and carcinoma was found (2/40, 3/40, 4/40, 13/40 in the 0.1, 0.5, 2.5, and 12,5 mg/kg urethane dose groups, respectively vs. 2/40 in the 0.1 mg/kg urethane dose group, $p = 0.0016$ by Fisher's exact test). The incidence data for the untreated control animals were lost. The trend was found to be dose-related ($p < 10^{-4}$ by Mantel-Haenszel trend test).

Klein *et al.* (1962) treated 7-8 day old $B6AF_1/J$ mice (C57BL/6 female × A/J male) with 2.8 or 5.5 mg urethane in 0.05 ml 0.1% dioctylester of sodium sulfosuccinic acid by oral gavage 3 times per week for 5 weeks. Control groups for the low-dose group included both males receiving vehicle only and males receiving no treatment. Males and females receiving no treatment served as a control for the high-dose group. Survivors of the treatment period comprised the study group and ranged from 39 to 57 animals. Survival in the treated groups was significantly lower than in controls. Among animals receiving the higher dose of urethane, treated males had a higher incidence of leukemias (32/42 treated vs. 0/38 vehicle controls, $p = 10^{-13}$; Fisher's exact test), lung adenomas (42/42 treated vs. 10/38 vehicle controls, $p = 10^{-12}$) and hepatoma (4/42 treated vs. 0/38 vehicle controls, $p = 0.07$) than animals receiving vehicle alone. Among animals receiving the lower dose of urethane, males showed a higher incidence of lung adenomas (40/41 treated vs. 3/40 untreated controls, $p = 10^{-17}$), hepatoma (23/41 treated vs. 0/40 untreated controls, $p = 10^{-8}$), and leukemias (19/41 treated vs. 0/40 untreated controls, $p = 10^{-6}$) relative to untreated control animals. In the same dose group, females showed a higher incidence of leukemias (16/40 treated vs. 1/57 controls, $p = 10^{-6}$) , lung adenomas (39/40 treated vs. 9/57 controls, $p = 10^{-6}$), hepatomas (5/40 treated vs. 0/57 controls, $p = 0.01$), and forestomach papillomas (3/40 treated vs. 0/57 controls, $p = 0.07$) relative to untreated control animals.

Della Porta *et al.*(1963a) exposed 5 groups of male and female CTM mice to drinking water containing 0.4% urethane in several exposure scenarios ranging from a total exposure time of 5 to 15 days. Effective group size was the number of survivors at 25 weeks for treated animals (range: 30-83 mice) and survivors at 45 weeks for controls (88 males and 99 females). Among all exposed animals there was a significant increase in the incidence of lung adenomas over control animals ($p < 10^{-8}$; Fisher's exact test). Among all exposed female mice, the incidence of lymphosarcoma was increased over controls ($p < 0.05$). Among all exposed male mice, the incidence of reticulosarcoma was increased over controls ($p < 0.04$). Other tumor types showing

some significant increase ($p < 0.05$) in incidence over controls in some but not all exposure scenarios include lymphosarcomas and Harderian gland adenomas in male mice, and mammary gland adenocarcinoma, hepatoma, and Harderian gland adenomas in female mice.

Table 1. Tumor incidence in CTM mice exposed to drinking water containing 0.4% urethane (Della Porta *et al.*, 1963a).

	A*		B		C		D		E		control	
tumor type	male	female	male	female	male	female	male	female	male	female	male	female
lung adenoma	29/36	53/63	42/56	53/83	58/71	51/68	19/45	26/48	25/30	30/39	2/88	7/99
lympho-sarcoma	12/36	17/63	14/56	13/83	14/71	15/68	8/45	7/48	2/30	10/39	4/88	5/99
reticulo-sarcoma	3/36	4/63	6/56	1/83	8/71	6/68	3/45	2/48	3/30	2/39	0/88	7/99

*Exposure scenarios: A - two 10 day exposures, separated by 10 days; B - one 10 day exposure; C - three 5 day exposures, separated by 10 days; D - two 5 day exposures, separated by 10 days; E - one 5 day exposure.

Della Porta *et al.* (1963b) conducted another study similar to that described above, but exposed CTM mice (75 male and 108 female) to drinking water containing 0.4% urethane for 10 days or two 10-day periods separated by 10 days. Control animals received plain drinking water (130 males and 120 females). Surviving animals were sacrificed at 75 weeks. The effective group size was considered the size of the group at the time of appearance of the first malignant lymphoma. Among male and female mice in both treatment groups, the incidence of malignant lymphoma was elevated over control animals (15/40 in the 20-day treatment group, 19/61 in the 10-day treatment group, vs. 4/103 controls, $p < 10^{-4}$ by Fisher's exact test). Among female mice, the incidence of mammary gland tumors was increased over controls (21/70 in the 20-day treatment group vs. 15/108 controls,$p < 0.008$; 34/83 in the 10-day treatment group vs. 15/108 controls, $p = 10^{-4}$). Other tumors observed included lung adenomas, mammary carcinomas, liver angiosarcomas, hepatomas, Harderian gland adenomas, and forestomach and skin papillomas.

Della Porta *et al.* (1967) exposed four inbred mouse strains (C57BL, C3H, C3Hf, SWR) and one hybrid mouse strain ($B6C3F_1$) to drinking water containing 0.4% urethane. Five-week old male and female animals were exposed for 15-20 days in 5- or 10-day periods separated by 10 days, and 10-day old animals were exposed five times, once every other day. The effective group size for analysis of tumor incidence was considered the initial number of animals less those dying without tumors before the 25th week for urethane-exposed animals or the 45th week for control animals. The effective group size ranged from 30 to 158 animals for animals showing significant increases in tumor incidence. Among male and female $B6C3F_1$ mice exposed for 10 days, the incidence of Harderian gland tumors (45/51 exposed vs. 3/32 control, males; 44/81 exposed vs. 0/39 control, females; $p < 10^{-10}$, Fisher's exact test) and lung adenomas (23/51 exposed vs. 7/32 control, males; 18/81 exposed vs. 4/39 control, females; $p < 0.1$) was increased. Among female $B6C3F_1$ mice alone, the incidence of thymic lymphosarcoma (10/81 exposed vs. 0/39 control; $p = 0.02$) and mammary gland adenocarcinoma (23/81 exposed vs. 1/39 control; $p = 10^{-3}$) was also increased. Among male and female C3Hf mice exposed for 15 days, the incidence of lung adenoma (45/79 exposed vs. 3/30 control, males, $p = 10^{-5}$; 46/87 exposed vs. 12/62 control, females, $p = 10^{-4}$) and Harderian gland adenoma (32/79 exposed vs. 3/30 control, males, p =

0.001; 25/87 exposed vs. 2/62 control, females, $p = 10^{-4}$) was increased. Among female C3Hf mice alone, the incidence of mammary adenocarcinoma (36/87 exposed vs. 6/62 control; $p = 10^{-5}$), thymic lymphosarcoma (2/87 exposed vs. 0/39 control; $p = 0.02$), and hepatoma (29/87 exposed vs. 15/62 control; $p = 0.15$) was increased.

Innes *et al.* (1969) treated male and female $B6C3F_1$ and $B6AKF_1$ mice (24/sex) with 158 mg/kg body weight urethane (on day 7) by oral gavage from day 7 to 28 of life. Thereafter, animals were exposed to a concentration of 600 ppm urethane in their diet. Control groups (90/sex/strain) received received vehicle alone, then normal diet. Surviving animals were sacrificed and autopsied between 78 and 88 weeks of age. Significant increases in the incidence of pulmonary adenomas or carcinomas and hepatomas were observed in treated animals of both sexes and strains (see Table 2, $p < 0.05$, Fisher's exact test). The incidence of angiomas was increased in male and female $B6AKF_1$ mice ($p < 0.01$). Harderian gland adenomas were increased in $B6C3F_1$ females and $B6AKF_1$ males and females ($p < 0.01$). Lymphomas were increased in $B6AKF_1$ male mice ($p < 0.01$).

Table 2. Tumor incidence data on two strains of mice exposed to urethane by oral gavage and in drinking water (Innes, 1969).

	$B6C3F_1$				$B6AKF_1$			
	male		female		male		female	
tumor type	treated	control	treated	control	treated	control	treated	control
pulmonary adenomas or carcinomas	6/20	5/79	6/23	3/87	15/22	10/90	17/19	3/82
hepatomas	8/20	8/79	12/23	0/87	14/22	5/90	5/19	1/82
angiomas					4/22	0/90	11/19	0/82
Harderian gland adenomas			5/23	4/87	11/22	0/90	7/19	0/82
lymphomas					6/22	1/90		

Tomatis *et al.* (1972) report on a study in which urethane treatment was used as a positive control in a study of DDT's long-term health effects. Male and female CF-1 mice (60/sex) were exposed continuously to drinking water containing 0.01% urethane for 6 generations. Control animals (60/sex) were given plain drinking water. Parent generation animals were sacrificed at 140 weeks and subsequent generations at 130 weeks. Survival among animals of both sexes was reduced by urethane treatment. For statistical purposes, group size was determined by the number of animals surviving at the time of the appearance of the first tumor of any type. Comparison of groups was made by combining data from all generations. Lung tumor incidence was found to be significantly increased in urethane treated male mice (261/314 exposed vs. 157/328 controls, $p = 10^{-21}$, Fisher's exact text) and female mice (181/241 exposed vs. 124/340 controls, $p = 10^{-20}$). Among treated males, lymphoma incidence was increased (100/314 exposed vs. 79/328 controls, $p = 0.02$) and among treated female mice, osteoma incidence was increased (55/241 exposed vs. 39/340 controls, $p < 0.001$).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Although IARC (1988) has recognized urethane as a possible human carcinogen, inadequate information relating cancer incidence to specific exposure levels precludes the development of a cancer potency value from human data. An abundant body of literature relating urethane exposure to the development of tumors in animals is available. Standard carcinogenesis models applied to the data, along with some data useful for making pharmacokinetic adjustments, permit quantitative estimates of cancer potency from the animal studies. Estimated potency values are summarized below along with the rationale for development of the reference unit risk value.

Methodology

Estimates of cancer potency from the available data on the carcinogenicity of urethane can be made based on the multistage model initially described by Armitage and Doll (1954). For studies in which variable dosing over time has occurred, a mathematical dosage modification was made based on the estimation procedures described by Crouch (1983) and Crump and Howe (1984). Several studies have been conducted which also permit making pharmacokinetic adjustments in the estimation of carcinogenicity. Specifically, a model has been developed describing the pharmacokinetics of urethane either administered continuously or in discrete increments (Mitchell and Gauthier Associates Inc., 1975). Urethane distribution in the body and kinetic constants for rats and mice have been determined from the studies of O'Flaherty and Sichak (1983) and Nomeir *et al.* (1989). When appropriate, a proportional correction factor was applied to the experimental dose rate to estimate the effective dose rate.

Estimates of human cancer potency (q_{human}) were estimated from derived animal values (q_{animal}) based on a scaling factor proportional to the third power of the human to experimental animal body weight ratio (bw_h and bw_a). The relationship is described as follows:

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

Table 3 presents the estimated human cancer potency values from animal studies in which significantly increased in tumor incidences have been found, including the species studied, most sensitive site of tumor development, the multistage model applied to the incidence data, and whether a pharmacokinetic adjustment was applied. For details of the methodology and assumptions made in deriving the potency, see Salmon and Zeise (1991). A measure of the "expected" or "average" value of the potency (q_1) estimated from the experimental data, termed q_{bar} , is also presented. The q_{bar} is derived when there are a large number of positive data points and the probability mass function (arithmetic mean) becomes less meaningful. It is derived by numerical computation, using the same continuous, asymptotic distribution as when deriving the upper confidence limit. The q_{bar} value is derived as follows,

$$q_{bar} = \int_0^\infty f(q_1) \cdot q_1 \, dq_1$$

with $f(q_1)$ as the frequency distribution whose log-likelihood function follows a chi-square distribution.

The selection of a cancer potency value should be made on the basis of the most sensitive site, species, and study, in the absence of evidence that such a value is not representative. The hamster studies of Pietra and Shubik (1960) and Toth *et al.* (1961a, 1969) indicate the hamster may not be as sensitive as the mouse when individual tumor sites are compared. Although the limited data available do not rule out the possibility that the hamster may be the more sensitive species, data are not available to make quantitative comparisons of hamsters and mice. This, coupled with the fact that there are extensive studies on mice, suggests the mouse urethane studies are more appropriate than hamster studies in developing a cancer potency value. Only two studies in the rat are useful for deriving cancer potency values. The Tannebaum *et al.* (1962) study showing development of Zymbal's gland tumors is of limited use since there is no supporting evidence that this site of tumor development is the most sensitive. The Schmähl *et al.* (1977) study is also of questionable value because of incomplete reporting of tumor incidence in untreated animals, in spite of showing sensitive induction of mammary tumors in female rats. In light of these limits on the studies in hamster and rats, the body of data showing tumor induction in mouse has been deemed most appropriate for the development of a cancer potency value.

Calculation of the geometric mean of q_{human} and q_{bar} values from the most sensitive sites of malignancy development in the oral mouse studies resulted in values of 0.5 and 1.4 $(mg/kg\text{-}day)^{-1}$, respectively. The geometric mean of the q_{bar} values provides an estimate of the upper 95% confidence limit on the distribution of values. Calculation of the geometric mean of q_{human} and q_{bar} values from mouse studies where the lung was the most sensitive site of malignancy development resulted in values of 0.8 and 1.9 $(mg/kg\text{-}day)^{-1}$, respectively. These mean values, coupled with the q_{human} values from the sensitive multiple dose study by Schmähl *et al.* (1977), indicate the most plausible estimate of cancer potency for urethane falls in the range of 0.6 to 3.0 $(mg/kg\text{-}day)^{-1}$. Therefore, as a reasonable estimate to the cancer potency, 1.0 E+0 $(mg/kg\text{-}day)^{-1}$ has been adopted as a cancer potency value.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.9 E-4 $(\mu g/m^3)^{-1}$.

Table 3. Cancer potency estimates from oral studies in animals (adapted from CDHS (1989)).

study/tumor	species/strain	sex	model*	q_{human} (95 %) $(mg/kg\text{-}day)^{-1}$	q_{bar} $(mg/kg\text{-}day)^{-1}$
Pietra (1960)	hamster/ Syrian G		MST		
skin melanotic tumor		M		0.19	0.11
forestomach papilloma		M		0.11	0.060
forestomach papilloma		F		0.18	0.094
Toth (1961a)	hamster/Syrian G		AD		
forestomach papilloma		M		0.13	0.091
forestomach papilloma		F		0.15	0.11
Toth (1969)	hamster/Syrian G		MST		
forestomach papilloma		M		0.10	0.077
forestomach papilloma		F		0.20	0.15
Tannenbaum (1962)	rat/Sprague-Dawley		MPK		
Zymbal gland carcinoma		M		0.12	0.061
Schmähl (1977)	rat/Sprague-Dawley		WPK		
mammary gland carcinoma		F		0.83	0.48
Toth (1961b)	mouse/Swiss		APK		
lung adenoma		M		3.8	3.0
lung adenoma		F		3.6	2.9
lymphoma		M		0.30	0.18
lymphoma		F		0.46	0.25
Tannenbaum (1962)	mouse/		APK		
lung alveolar cell tumor	DBA	M		0.9	0.61
mammary gland carcinoma	DBA	F		1.2	0.90
lung adenoma	DBA	M		0.4	0.29
lung adenoma	C3H	F		0.4	0.28
Klein (1962)	mouse/$B6AF_1$		APK		
lung adenoma		M		0.85	0.54
lung adenoma		F		0.76	0.48
leukemia		M		0.090	0.071
leukemia		F		0.10	0.066
Della Porta (1963a)	mouse/CTM		APK		
lung adenoma		M		0.62	0.17
lung adenoma		F		0.60	0.12
Della Porta (1963b)	mouse/CTM		APK		
malignant lymphoma		M		0.55	0.17
mammary gland		F		0.50	0.12
Della Porta (1967)	mouse/		APK		
Harderian gland tumor	$BC3F_1$	M		0.88	0.66
Harderian gland tumor	$BC3F_1$	F		0.32	0.25
Harderian gland tumor	C3Hf	M		0.22	0.15
Harderian gland tumor	C57BL	M		0.32	0.25
Harderian gland tumor	C57BL	F		0.23	0.19
mammary gland carcinoma	C3Hf	F		0.23	0.16
lung adenoma	C3H	M		0.18	0.13
lung adenoma	SWR	M		0.94	0.67
lung adenoma	SWR	F		1.0	0.76

Table 3. Cancer potency estimates from oral studies in animals (continued) (adapted from CDHS (1989)).

study/tumor	species/strain	sex	model*	q_{human} (95 %) $(mg/kg\text{-}day)^{-1}$	q_{bar} $(mg/kg\text{-}day)^{-1}$
Innes (1969)	mouse/		MPK		
liver hepatoma	$B6C3F_1$	M		0.40	0.23
liver hepatoma		F		0.61	0.27
lung adenoma	$B6AKF_1$	M		0.78	0.51
lung adenoma		F		1.5	0.99
Tomatis (1972)	mouse/CF-1		MPK		
lung adenoma		M		0.90	0.75
lung adenoma		F		0.67	0.55
Schmähl (1977)	mouse/NMRI				
lung adenoma		M	WPK	3.0	1.7
lung carcinoma		M	MPK	0.85	0.55
lung adenoma		F	WPK	1.9	-
lung carcinoma		F	MPK	0.56	0.12
			W1PK	3.0	1.7

*MST- multistage; APK - Armitage-Doll model; MPK - multistage with pharmacokinetic adjustment; WPK - Weibull time-dependent with pharmacokinetic adjustment; W1PK - Weibull linear in dose time-dependent model with pharmacokinetic adjustment.

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TECHNICAL SUPPORT DOCUMENT FOR DETERMINING CANCER POTENCY FACTORS
APPENDIX A

TOXICITY EQUIVALENCY FACTORS FOR POLYCHLORINATED DIBENZO-p-DIOXINS AND DIBENZOFURANS

Introduction

The Office of Environmental Health Hazard Assessment (OEHHA) cancer potency value for 2,3,7,8- tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) was determined as part of the Toxic Air Contaminant Program and approved by the Scientific Review Panel and the Air Resources Board in 1986 (CDHS, 1986). To evaluate the cancer risk due to exposure to samples containing mixtures of polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), California Toxicity Equivalency Factors (CTEFs) were developed and adopted (CDHS, 1986). These factors were based on rodent cancer bioassay data on 2,3,7,8-TCDD and a mixture of hexaCDDs and assumptions about the relative potency of other PCDDs and PCDFs that had not undergone cancer bioassays. Since 1986, another TEF scheme was developed during an international symposium (NATO/CCMS, 1988a,b), and it has been adopted by US EPA (US EPA, 1989) and the Department of Toxic Substances Control (DTSC) (DTSC, 1992). The international scheme, referred to as ITEFs, is based on experimental cancer and noncancer data for many 2,3,7,8-PCDDs and 2,3,7,8-PCDFs and on the assumption that the mechanism of all PCDD/PCDF-related biologic effects are based on initial binding to a specific protein, the Ah receptor. Because the ITEF scheme incorporates more experimental data from cancer and noncancer studies for more PCDDs/PCDFs than does the CTEF scheme, the replacement of the CTEFs by the ITEFs is appropriate for use in risk assessment. This approach also increases uniformity among Cal/EPA guidelines.

Background

PCDDs and PCDFs belong to a series of tricyclic aromatic hydrocarbons, in which the middle ring contains one (PCDF) or two (PCDD) ring oxygens. On each of the other two rings, four sites are available for substitution (eight sites total). There are 75 possible chlorinated PCDD congeners and 135 possible chlorinated PCDF congeners. (Rabbe *et al*., 1979). Congeners of PCDD and PCDF which contain chlorine in the same position are referred to as homologues. For example, 2,3,7,8-tetrachlorodibenzofuran (2,3,7,8-TCDF) is a homologue of 2,3,7,8-TCDD.

The original public health concern about the PCDDs/PCDFs was the result of high toxicity of 2,3,7,8-TCDD. In particular, the concern about the carcinogenicity of 2,3,7,8-TCDD led to the development of a cancer potency by the California Department of Health Services (CDHS), for this congener (CDHS, 1986). Additional studies showed, however, environmental samples containing 2,3,7,8-TCDD contained other congeners which were also toxic (NATO/CCMS, 1988a,b; US EPA, 1989). The toxic and biologic responses to the PCDDs/ PCDFs are varied and include carcinogenicity, immunotoxicity, reproductive toxicity, thymic atrophy, decreased body

weight gain, increased cytochrome P450-dependent activity, cell proliferation and liver damage. The current working hypothesis for the mechanism of the origin of the disease state associated with exposure to PCDD/PCDF is the required binding of the PCDD or PCDF congener to a specific receptor protein (the Ah receptor) followed by the expression of various endpoints (CDHS, 1986; NATO/CCMS, 1988a,b; US EPA, 1989). While continued research on the toxicities associated with each of the 210 congeners, including dose-response assessments, would lead to important toxicologic information, the cost and time would lead to delays in addressing the public health concerns associated with exposures to these mixtures. Hence, a means for expressing exposure related health risk of PCDD/PCDF mixtures needs to be developed in the absence of a complete data base.

Toxicity Equivalency Factors

Toxicity equivalency factors (TEFs) are numerical factors that express the toxicity of an individual PCDD or PCDF relative to the toxicity of TCDD, the highly toxic and best studied among the 210 congeners. TEFs are used in risk assessment to calculate the potential for health effects from a mixture of PCDDs and PCDFs. The total "2,3,7,8-TCDD" equivalents - referred to as TCDD equivalents - in a sample (e.g. air, soil, food) is estimated by multiplying the concentration of each congener in the sample by its appropriate TEF and summing all TCDD equivalents. The total TCDD equivalents (TEQ) is then used in conjunction with a cancer potency or reference exposure level to estimate cancer risk or noncancer hazard index, respectively.

Although analytical methods are currently available to reliably quantify the amount of the various congeners in a sample, not all congeners of PCDD and PCDF possess equal biologic activity. Such differences may be a reflection of different toxicokinetic properties. For example, congeners that lack the 2,3,7,8-configuration of chlorine groups, do not appear to bioaccumulate, as do the 2,3,7,8-congeners. Within the group of 2,3,7,8-congeners, biologic activity is variable, and this property is probably due to differences in dose-response relationships. A basic premise of the TEF methodology is the presence of a common biologic end-point or in the case of multiple end-points, a common mechanism of action. A second assumption is additivity of effects. These assumptions are inherent in all TEF-schemes, and the accuracy of all TEF-schemes will be affected by situations where such assumptions are not applicable.

California TEFs (CTEFs)

TEF schemes for PCDDs and PCDFs have been developed or adopted by many governmental institutions throughout the industrialized world (NATO/CCMS, 1988). Among the schemes was one developed by the CDHS, based on carcinogenicity data (CDHS, 1986) and adopted for use in the California Toxic Air Contaminant Program and in the California Air Toxics "Hot Spots" Program (CAPCOA, 1992). This scheme is referred to as the CTEF. Due to lack of data on the 2,3,7,8-penta- and hepta- congeners of PCDD, the carcinogenic potencies of the penta-congeners were considered equal to that of TCDD (1.0) and that of the hepta-congeners equal to that of hexaCDD (0.03), relative to 2,3,7,8-TCDD. The 2,3,7,8-PCDFs were considered equal in cancer

potency to their PCDD homologues. The potencies of the octa-congeners of PCDD and PCDF were assumed to be zero, based on the evidence available at the time, that the octa-chlorinated compounds did not produce characteristic toxicity following short-term exposure.

International TEFs (ITEFs)

The ITEF scheme was the result of an international conference, convened for the purpose of reaching a consensus for a uniform TEF scheme based on available whole animal non-cancer and cancer data, short term and in vitro data (NATO/CCMS, 1988a,b). To incorporate the results from many studies, the ITEF scheme used the assumption that all effects are initiated by the interaction of a PCDD or PCDF congener with a specific receptor protein, the Ah receptor. The rationale for this assumption comes from analyses in which biologic endpoints (i.e. body weight loss, thymic atrophy, *in vivo* enzyme induction) were found to be highly correlated with known Ah receptor associated effects (e.g. increased cytochrome P450-dependent enzyme activity in vivo and binding affinities). The ITEF scheme focuses on those congeners that are preferentially absorbed and accumulated in mammalian tissue over a long period of time and exhibit a similar spectrum of toxicities as 2,3,7,8 TCDD, i.e. PCDDs/PCDFs that in which positions 2-,3-,7-, and 8- are substituted by chlorine. Unlike the CTEF scheme, the octa-congeners are included in the ITEF scheme, because of a study in which rats exposed to OCDD, exhibited 2,3,7,8,-TCDD-like non-cancer toxicities after a 13-week exposure (Couture *et al*., 1988). This study was not available at the time the CTEFs were developed.

The choice of an ITEF for each 2,3,7,8-PCDD/PCDF congener was based on a synthesis of data from cancer studies, long-term toxicity studies, subchronic effects including thymic atrophy and body weight loss, acute toxicity studies and receptor binding and enzyme induction. Greater weight was given to results from long-term studies, but information of short-term studies was also considered. In the absence of long-term studies, data from short-term whole animal and/or *in vitro* studies were used. A specific formula was not applied to the various data, but rather the final individual ITEF was based on the professional judgment of the aggregate data available for the individual congener.

The basis for the ITEF scheme has been extensively reviewed by US EPA (US EPA, 1989) and the California Department of Toxic Substances Control (DTSC, 1992). These agencies concluded that the ITEF scheme was superior to the CTEF scheme because of the larger, more inclusive data base. The US EPA and the DTSC each adopted the ITEF scheme for use in risk assessment activities as an interim procedure which is expected to be updated as more information becomes available.

Comparison of CTEF and ITEF Schemes

Based on the assumption that the PCDD/PCDF induced biologic effects result from an interaction between a congener and the Ah receptor, the carcinogenicity driven CTEFs may be compared to the ITEFs based on non-cancer and cancer end points. The CTEF and ITEF schemes are outlined in Tables 1 and 2. Table 1 describes, qualitatively, the features of the two methodologies. Included in Table 2 are the ranges of values associated with the many end-points

for each congener in the ITEF scheme. TEFs for two major noncancer toxicity endpoints, teratogenicity and immunotoxicity, are presented in Table 3. An important feature of this table is the relatively high toxicity of the 2,3,4,7,8-pentaCDF, based on teratogenicity (TEF = 0.1) and immunotoxicity (TEF = 0.8).

A comparison of the CTEF and ITEF schemes (Table 2) shows the CDHS to ITEF ratios are variable. For example, the CTEF/ITEF for 1,2,3,7,8-pentaCDF is 20, whereas the same ratio for the 2,3,7,8-hexaCDD and hexaCDF congeners is 0.3. In each case, the CTEF was based on an assumed equivalence of carcinogenicity, whereas the ITEF was based on experimental data from cancer and noncancer studies. For the octa-congeners of PCDD and PCDF, the ITEF value is 0.001 whereas no TEF was developed for the CTEF scheme. Although the ITEF = 0.001 is small, its use in the ITEF scheme recognizes a heretofore unknown toxicity property of the octa congeners.

The ultimate use of a TEF scheme is to estimate the TEQ level in a sample. Therefore, a comparison of TEQs in various environmental samples, as estimated by the CTEF and ITEF schemes, is of interest. In Table 4, the TEQs, present in seven contaminated samples, are compared by the CTEF and ITEF methodologies. The results suggest that where differences occur, they are less than 10-fold and appear to be due largely to differences in the TEFs for the PCDFs, in particular the tetra- and penta-congeners. When studying the results in Table 4, the reader should keep in mind the ITEF scheme was developed from a much larger data base than the CTEFs. The CTEF scheme also assumes the 2,3,7,8-penta congeners are equivalent to 2,3,7,8-TCDD, the 2,3,7,8-hepta-congeners are equivalent to the 2,3,7,8-hexa-congeners, and the PCDFs are equivalent to their PCDD homologues. In the ITEF schemes, such assumptions are not made but are based on available information.

Public Health Impact

Currently, two schemes, the CTEFs and the ITEFs, are in use in the State of California for risk assessment of PCDD/PCDF contaminated samples. The CTEF scheme was incorporated into the Hot Spots Risk Assessment Guidelines (CAPCOA, 1993), while the ITEF scheme was adopted by the DTSC (DTSC, 1992). The ITEF scheme incorporates more data on congener specificity and multiple end-points. The use of multiple endpoints is important for PCDD- and PCDF-induced toxicities, because the evidence is clear that exposure to this class of compounds leads to many responses that may be related by a similar mechanism of action, i.e. initial binding to the Ah receptor. Hence, the ITEF scheme provides a more complete picture of the relative toxicity of the various congeners than does the CTEF scheme. Since the TEFs are applied to carcinogenic and noncancer evaluations in risk assessment, the ITEF scheme is more appropriate than the CTEF scheme.

The results of the two schemes are relatively consistent. Although the CTEF scheme sometimes results in TEQs up to 4-times greater than the ITEF scheme, the differences in the TEQs are generally within the uncertainties of the estimated carcinogenicity or noncancer toxicity of

2,3,7,8-TCDD. Consequently, the impact using the ITEFs in place of the CTEFs to estimate PCDD/PCDF exposure related risk, will be minimal.

The user of any TEF scheme should not consider such a methodology as definitively precise analysis for PCDD/PCDF related adverse health effects. A TEF scheme is an instrument that is useful for estimating health risks but it contains uncertainties shared by all risk assessment methodologies. Furthermore, as research results become available, changes in our understanding of the basis of PCDD/PCDF related health effects may result in changes to the TEF scheme (see e.g. US EPA, 1989; Maronpot *et al*., 1993; DeVito and Birnbaum, 1995).

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Table 1

FEATURES OF THE CTEF AND ITEF METHODOLOGIES

	CTEF	ITEF
Congeners of Concern	2,3,7,8-	2,3,7,8-
Available Data	Tetra-, Hexa-	Tetra-, Penta-, Hexa-, Hepta- Octa-
Biologic Endpoint	Carcinogenicity	Acute,chronic toxicity, carcinogenicity
Application	Assess mixtures for cancer & noncancer risk	Assess mixtures for cancer & noncancer risk

Table 2

TOXICITY EQUIVALENCY FACTORS [a]

DIBENZO-p-DIOXINS & DIBENZOFURANS

(relative to 2,3,7,8-TCDD)

COMPOUND	CONGENERS	DHS - TEF[b]	I-TEF[c]	Obs. TEF Toxicity[d]	Obs. TEF AHH Ind. cell[d]	Obs. TEF AHH Ind. animal[d]
Dioxins						
Mono-, Di-, Tri-CDDs		0	0			
TCDD	2,3,7,8- others	(1.0) 0	(1.0)	(1.0)	(1.0)	(1.0)
PeCDD	2,3,7,8- others	1.0 0	0.5 0	0.05 - 0.6	0.1	0.006 - 0.01
HxCDD	2,3,7,8- others	0.03 0	0.1 0	0.02 - 0.2	0.1	0.008 - 0.05
HpCDD	2,3,7,8- others	0.03 0	0.01 0			0.003
OCDD		0	0.001		0.0002	0.0006
Dibenzfurans						
Mono-, Di-, Tri- CDFs		0	0			
TCDF	2,3,7,8- others	1.0 0	0.1 0	0.02 - 0.2	0.006	0.02 - 0.09
PeCDF	1,2,3,7,8- 2,3,4,7,8- others	1.0 1.0 0	0.05 0.5 0	0.02 - 1.0 0.05 - 0.8	0.003 - 0.05 0.1 - 0.2	0.03 - 0.06 0.3 - 1.4
HxCDF	2,3,7,8- otheres	0.03 0	0.1 0	0.01 - 0.2	0.01 - 0.02	0.04 - 0.5
HpCDF	2,3,7,8- others	0.03 0	0.01 0			
OCDF		0	0.001			

a. Endpoints include inhibition of body weight gain, thymic atrophy, hepatic arylhydrocarbon hydroxylase activity, ethoxyresorufin (sic) deethylase activity, lethality, teratogenicity, immunotoxicity, carcinogenicity.
b. CDHS (1986). Endpoint is carcinogenicity.
c. NATO/CCMS (1988) - adopted by USEPA (1989) and CTSCP (1991-draft)
d. NATO/CCMS (1988) - taken from Table 8, p.35.

Table 3

TEFs for PCDF CONGENERS BASED ON NON-CANCER

***IN VIVO* ED_{50} VALUES**

(relative to 2,3,7,8-TCDD)

	Endpoints	
Congeners	Teratogenicity	Immunotoxicity
2,3,7,8-TCDD	(1.0)	(1.0)
2,3,7,8-tetraCDF	0.05	0.2
1,3,6,8-tetraCDF		0.0007
2,3,4,7,8-pentaCDF	0.1	0.8
1,2,3,7,8-pentaCDF	0.03	
2,3,7,8,-tetraCDF	0.05	0.2
1,2,3,7,9-pentaCDF		0.003
1,2,3,4,7,8-hexaCDF	0.01	

a. Calculated from data presented in Table 5 (NATO/CCMS, 1988).

Table 4

A COMPARISON OF CTEF- AND ITEF- BASED TCDD EQUIVALENTS IN PCDD/PCDF MIXTURES FOUND IN SELECTED SAMPLES,

	TCDD Equivalents (CTEF / ITEF)[a]		
Source of Contamination	PCDDs	PCDFs	PCDDs + PCDFs
Metal Recovery Fly Ash[b]	1.1	4.0	3.9
PCB Soot Fire[c]	1.6	1.5 - 4.2[d]	1.5 - 4.1[d]
MSW - ESP Dust[c]	0.85	1.8 - 3.5[d]	1.5 - 2.4[d]
Contaminated Soil[e]	1.0	2.2	1.7
Ground Beef[f]	1.09	1.4	1.4
Soft Cream Cheese[f]	1.2	1.8	1.4
Haddock[f]	1.0	4.5	2.6

a. The TCDD equivalents are calculated by multiplying the concentration of ezch congener by its CTEF or ITEF and summing values for PCDDs only, PCDFs only, and PCDDs + PCDFs.

b. from Harnly *et al*., (1992).

c. from USEPA (1989).

d. The chemical analyses of the penta-PCDFs did not distinguish between 1,2,3,7,8- and 2,3,4,7,8-PCDF, to which different ITEFs have been assigned from DTSC (1991).

e. from DTSC (1991).

f. from Schecter *et al*., (1994).

TECHNICAL SUPPORT DOCUMENT FOR DETERMINING CANCER POTENCY FACTORS

APPENDIX B

TOXIC AIR CONTAMINANT DOCUMENTS

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TECHNICAL SUPPORT DOCUMENT FOR DETERMINING CANCER POTENCY FACTORS

APPENDIX C

International Agency for Research on Cancer (IARC) and U.S. Environmental Protection Agency (US EPA) Carcinogen Classifications

International Agency for Research on Cancer (IARC) Carcinogen Classifications (IARC, 1987)

Group 1: The agent is carcinogenic to humans.

This category is used only when there is sufficient evidence of carcinogenicity in humans.

Group 2

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as agents for which, at the other extreme, there are no human data but for which there is experimental evidence of carcinogenicity. Agents are assigned to either 2A (probably carcinogenic) or 2B (possibly carcinogenic) on the basis of epidemiological, experimental and other relevant data.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. Exceptionally, an agent may be classified into this category solely on the basis of limited evidence of carcinogenicity in humans or of sufficient evidence of carcinogenicity in experimental animals strengthened by supporting evidence from other relevant data.

Group 2B: The agent is possibly carcinogenic to humans.

This category is generally used for agents for which there is limited evidence in humans in the absence of sufficient evidence in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in humans or when human data are nonexistent but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent for which there is inadequate evidence or no data in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

Agents are placed in this category when they do not fall into any other group.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is evidence suggesting lack of carcinogenicity in humans together with evidence suggesting lack of carcinogenicity in experimental animals. In some circumstances, agents for which there is inadequate evidence of or no data on carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

U.S. Environmental Protection Agency (US EPA) Carcinogen Classifications (US EPA, 1986)

Group A: Human Carcinogen

This group is used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer.

Group B: Probable Human Carcinogen

This group includes agents for which evidence of human carcinogenicity based on epidemiologic studies is "limited," and also includes agents for which the weight of evidence of carcinogenicity based on animal studies is "sufficient." The group is divided into two subgroups. Usually, Group B1 is reserved for agents showing limited evidence of carcinogenicity from epidemiologic studies. It is reasonable, for practical purposes, to regard an agent with "sufficient" evidence of carcinogenicity in animals as if it presented a carcinogenic risk to humans. Therefore, agents for which there is "sufficient" evidence from animal studies and for which there is "inadequate evidence" or "no data" from epidemiologic studies would usually be categorized under group B2.

Group C: Possible Human Carcinogen

This group is used for agents with limited evidence of carcinogenicity in animals in the absence of human data. It includes a wide variety of evidence, e.g., (a) a malignant tumor response in a single well-conducted experiment that does not meet conditions for sufficient evidence, (b) tumor responses of marginal statistical significance in studies having inadequate design or reporting, (c) benign (not malignant) tumors with an agent showing no response in a variety of short-term tests for mutagenicity, and (d) responses of marginal statistical significance in a tissue known to have a high or variable background tumor rate.

Group D: Not Classifiable as to Human Carcinogenicity

This group is generally used for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available.

Group E: Evidence of Noncarcinogenicity for Humans

This group is used for agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

The designation of an agent as being Group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

REFERENCES

International Agency for Research on Cancer (IARC) 1987. Overall Evaluations of Carcinogenicity: An Updating of *IARC Monographs* Volumes 1 to 42 In: IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Supplement 7. IARC, Lyon, France, pp. 31-32.

U.S. Environmental Protection Agency (US EPA) 1986. Guidelines for Carcinogen Risk Assessment, Federal Register 45 FR 79318.

TECHNICAL SUPPORT DOCUMENT FOR DETERMINING CANCER POTENCY FACTORS

APPENDIX D

Asbestos Quantity Conversion Factors

The unit risk factor for asbestos is listed in this document in units of 100 PCM fibers/m^3 [1.9 E-4 (100 PCM fibers/m^3)$^{-1}$] and in units of µg/m^3 [6.3 E-2 (µg/m^3)$^{-1}$]. The value listed in the Toxic Air Contaminant (TAC) document for asbestos (CDHS, 1986) was 1.9 E-4 (100 PCM fibers/m^3)$^{-1}$. However, emitted asbestos quantities reported to the various Air Quality Districts under the requirements of the Air Toxics "Hot Spots" Information and Assessment Act of 1987 (Health and Safety Code (HSC) Section 44300 et seq. and as amended by Statutes 1992, Chapter 1162) are in units of pounds/year and maximum pounds/hour. Therefore, the original TAC unit risk value has been converted using a factor of 0.003 µg asbestos = 100 asbestos fibers which has been derived from information published by US EPA (1985). The number of asbestos fibers associated with a given mass of asbestos can vary appreciably. Also, US EPA (1985) has stated that this conversion factor is the geometric mean of measured relationships between optical fiber counts and mass airborne chrysotile in several published studies, the range of the conversion factor between the different studies is large (0.0005 - 0.015 µg asbestos/100 asbestos fibers), and carries with it an appreciable uncertainty. Use of the unit risk factor listed in the asbestos TAC document [1.9 E-4 (100 PCM fibers/m^3)$^{-1}$], wherever possible, will result in a more precise risk estimation. Additionally, the unit risk factor expressed in units of (µg/m^3)$^{-1}$ may change if a conversion factor with less uncertainty is developed, or may be eliminated if asbestos quantity reporting requirements render use of a unit risk factor expressed in units of (µg/m^3)$^{-1}$ unnecessary.

REFERENCES

California Department of Health Services (CDHS) 1986. Report to the Air Resources Board on Asbestos. Part B. Health Effects of Asbestos. Epidemiological Studies Section, Berkeley, CA.

U.S. Environmental Protection Agency (US EPA) 1985. Airborne Asbestos Health Assessment Update. EPA/600/8-84/003F, Office of Health and Environmental Assessment, Washington, DC.

TECHNICAL SUPPORT DOCUMENT (TSD) FOR DETERMINING CANCER POTENCY FACTORS
APPENDIX E

US EPA IRIS INHALATION UNIT RISK AND ORAL CANCER POTENCY FACTORS FOR CHEMICALS LISTED IN THE TSD

Chemical	IRIS inhalation unit risk $(\mu g/m^3)^{-1}$	IRIS oral cancer potency factor (mg/kg-day)
Acetaldehyde	2.2E-6	NA
Acrylamide	1.3 E-3	4.5 E+0
Acrylonitrile	6.8 E-5	5.4 E-1
Aniline	1.6 E-6	5.7 E-3
Arsenic	4.3 E-3	1.5 E+0
Asbestos	2.3 E-1 (fibers/ml)	NA
Benzene	8.3 E-6	2.9 E-2
Benzidine	6.7 E-2	2.3 E+2
Benzo[a]pyrene	NA	7.3 E+0
Benzyl chloride	NA	1.7 E-1
Beryllium	2.4 E-3	4.3 E+0
Bis(2-chloroethyl) ether	3.3 E-4	1.1 E+0
Bis(chloromethyl)ether	6.2 E-2	2.2 E+2
1,3-Butadiene	2.8 E-4	NA
Cadmium (and compounds)	1.8 E-3	NA
Carbon tetrachloride	1.5 E-5	1.3 E-1
Chloroform	2.3 E-5	6.1 E-3
Chromium (hexavalent)	1.2 E-2	NA
3,3'-Dichlorobenzidine	NA	4.5 E-1
1,4-Dioxane	NA	1.1 E-2
Epichlorohydrin	1.2 E-6	9.9 E-3
Ethylene dibromide	2.2 E-4	8.5 E+1
Ethylene dichloride	2.6 E-5	9.1 E+2
Formaldehyde	1.3 E-5	NA
Hexachlorobenzene	4.6 E-4	1.6 E+0
Hexachlorocyclohexanes (technical grade)	5.1 E-4	1.8 E+0
Hydrazine	4.9 E-3	3.0 E+0
Methylene chloride	4.7 E-7	7.5 E-3
Nickel compounds	2.4 E-4	NA
N-Nitroso-n-dibutylamine	1.6 E-3	5.4 E+0
N-Nitroso-N-methylethylamine	NA	2.2 E+1
N-Nitrosodi-n-propylamine	NA	7.0 E+0
N-Nitrosodiethylamine	4.3 E-2	1.5 E+2
N-Nitrosodimethylamine	1.4 E-2	5.1 E+1
N-Nitrosodiphenylamine	NA	4.9 E+3
N-Nitrosopyrrolidine	6.1 E-4	2.1 E+0
Pentachlorophenol	NA	1.2 E-1
Propylene oxide	3.7 E-6	2.4 E-1
1,1,2,2-Tetrachloroethane	5.8 E-5	2.0 E-1
1,1,2-Trichloroethane (vinyl trichloride)	1.6 E-5	5.7 E-2
2,4,6-Trichlorophenol	3.1 E-6	1.1 E-2

TECHNICAL SUPPORT DOCUMENT FOR DETERMINING CANCER POTENCY FACTORS
APPENDIX F

HOT SPOTS CANCER UNIT RISK VALUES WHICH DIFFER FROM CORRESPONDING US EPA IRIS CANCER UNIT RISK VALUES

Chemical		Source	Hot Spots Unit Risk $(\mu g/m^3)^{-1}$	IRIS Unit Risk $(\mu g/m^3)^{-1}$	HS/IRIS Ratio
Acetaldehyde		TAC	2.7 E-6	2.2 E-6	1.2
Acrylonitrile		RCHAS-S	2.9 E-4	6.8 E-5	4.3
Arsenic (inorganic)	(inhalation)	TAC	3.3 E-3	4.3 E-3	0.8
Asbestos		TAC	6.3 E-2	7.7 E-3	8.2
			1.9 E-4[#]	2.3 E-5[#]	
Benzene		TAC	2.9 E-5	8.3 E-6	3.5
Benzidine		RCHAS-S	1.4 E-1	6.7 E-2	2.1
Bis(2-chloroethyl) ether		RCHAS-S	7.1 E-4	3.3 E-4	2.2
Bis(chloromethyl)ether		RCHAS-S	1.3 E-2	6.2 E-2	0.2
1,3-Butadiene		TAC	1.7 E-4	2.8 E-4	0.6
Cadmium (and compounds)		TAC	4.2 E-3	1.8 E-3	2.3
Carbon tetrachloride		TAC	4.2 E-5	1.5 E-5	2.8
Chloroform		TAC	5.3 E-6	2.3 E-5	0.2
Chromium (hexavalent)		TAC	1.5 E-1	1.2 E-2	12.5
3,3'-Dichlorobenzidine		RCHAS-S	3.4 E-4	1.3 E-4	2.6
1,4-Dioxane		RCHAS-S	7.7 E-6	3.1 E-6	2.5
Epichlorohydrin		RCHAS-S	2.3 E-5	1.2 E-6	19.2
Ethylene dibromide		TAC	7.1 E-5	2.2 E-4	0.3
Ethylene dichloride		TAC	2.2 E-5	2.6 E-5	0.8
Formaldehyde		TAC	6.0 E-6	1.3 E-5	0.5
Hexachlorobenzene		RCHAS-S	5.1 E-4	4.6 E-4	1.1
Hexachlorocyclohexanes (technical grade)		RCHAS-S	1.1 E-3	5.1 E-4	2.2
Methylene chloride		TAC	1.0 E-6	4.7 E-7	2.1
Nickel compounds		TAC	2.6 E-4	2.4 E-4	1.1
N-Nitroso-n-dibutylamine		RCHAS-S	1.1 E-1	1.6 E-3	68.8
N-Nitrosodiethylamine		RCHAS-S	1.0 E-2	4.3 E-2	0.2
N-Nitrosodimethylamine		RCHAS-S	4.6 E-3	1.4 E-2	0.3
N-Nitrosodiphenylamine		RCHAS-S	2.6 E-6	1.4 E-6	1.9
Pentachlorophenol		RCHAS-S	5.1 E-6	3.4 E-5	0.2
2,4,6-Trichlorophenol		RCHAS-S	2.0 E-5	3.1 E-6	6.5

Footnotes #: $[100\ PCM\ fibers/m^3]^{-1}$

Source Key

TAC Toxic Air Contaminant document, Office of Environmental Health Hazard Assessment (OEHHA)
RCHAS-S Standard Proposition 65 document, OEHHA
RCHAS-E Expedited Proposition 65 document, OEHHA

Note: The TSD Unit Risk and Cancer Potency Factors Table includes 12 US EPA IRIS cancer unit risk values.